ACTIVITY EVOKED IN THE VISUAL SYSTEM OF HUMAN, RHESUS MONKEY, AND CAT BY SPATIALLY PATTERNED AND NON-PATTERNED VISUAL STIMULI

By

HAROLD WILLIAM DODDINGTON

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ACTIVITY EVOKED IN THE VISUAL SYSTEM OF HUMAN, RHESUS MONKEY, AND CAT BY SPATIALLY PATTERNED AND NON-PATTERNED VISUAL STIMULI

By

Harold William Doddington

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Individual cells of visual cortex of cat and monkey have been shown to be specifically responsive to the size, location, and orientation of features in the visual field, while responses from human scalp have been shown to be sensitive to spatially patterned visual stimuli. To improve upon this loose relationship between what is known about animal visual systems and the data from humans, this research was designed to determine whether or not sensitivity of evoked responses from several locations within the visual system of animals (cat and rhesus monkey) to spatially patterned visual stimuli could be observed and, if so, to describe it in terms of the effect of pattern feature size, quality of focus, and repeatability.

Experiments were conducted with (1) attentive human, (2) behaviorally trained monkey, and (3) cat and monkey paralyzed with a neuromuscular blocking drug. Two methods were used. The behavioral training program, and the Maxwellian view instrument for visual stimulation of human subjects and paralyzed animals are unique and are described.

Two monkeys were trained. A rhesus trained to the visual fixation task well, and data from her indicated sensitivity of the evoked response to checkerboard patterned stimuli. A sootie mangabey did not train to the task well enough to be tested.

Data from human subjects demonstrated that the instruments and procedures used were effective for producing spatially patterned stimulation of the retina.

Cats with chronically implanted electrodes in the visual system were paralyzed, stimulated by projecting onto the central retinal area (1) an adaptation light with 30 degree diameter circular field and (2) diffuse or spatially patterned flash stimuli covering a 9 x 13.5 degree field, and their average responses recorded. On occasion individual responses were examined. These were not acute experiments. Recording sessions were 6 to 10 hours. Each animal recovered and could undergo additional recording sessions days or weeks later.

Results from paralyzed cats adapted to a dim photopic level are that the evoked responses from optic nerve and visual cortex are consistently sensitive to pattern stimulation. For equal energy stimulation of the retina, the responses to checkerboard patterned stimuli differ from those to non-patterned (diffuse) stimuli primarily in waveform, with small changes in overall amplitude. Response waveforms changed progressively with pattern feature size. The optic nerve response to 31, 55, and 79 minute patterns typically showed increased positivity at latencies of 30 to 60 msec, which is the late side of the primary positive peak. Difference waveforms (pattern

response - diffuse response) were extracted. Using defocused patterned stimulation, it was possible to obtain responses characteristic of diffuse stimulation.

Responses from epidural cortex electrodes on a rhesus under neuromuscular block demonstrate sensitivity to spatial pattern stimuli more vividly than do responses from cats. This monkey responded very well to a checkerboard pattern of size 11 minutes of arc per square. Response waveform changes were sufficient to cause the difference waveform to be larger in amplitude than the diffuse response. An 11 minute patterned stimulus defocused by 1.2 diopters produced a diffuse response.

The major conclusion of this dissertation is that animals can be used to study the sensitivity of evoked responses to spatially patterned visual stimulation at several levels within the visual system. Also, it was found that a given dioptric value of defocus was less effective in degrading responses to patterns of larger feature sizes than those of smaller feature sizes, which indicates that feature size and/or quantity of contrast border are of greater importance than contour sharpness in determining evoked activity.

INTRODUCTION

Statement of the Problem

Human visual pattern evoked responses which are generated by activity in the occipital cortex indicate that populations of cortical neurons respond differently to patterns with features of different shape, size, contrast, etc. It is unlikely that many single cell studies will ever be done on humans. To develop an understanding of how evoked responses which are sensitive to visual pattern information are generated, and of how a cell relates to the populations of which it is a part, it would be very desirable to determine whether or not an animal preparation can be used as a model for studying pattern sensitive evoked responses.

If such a model could be established, many experimental questions which could not be asked with humans could be investigated. Examples of these questions are: (1) From the receptive field structures of retinal ganglion cells and geniculate cells, and the sensitivity of ganglion cell responses to degree of focus of a retinal image, one might expect evoked responses from these stages prior to cortex to be modified by visual pattern information. Can such changes actually be detected? (2) Are the "cortical sources" which generate certain features of the evoked response localizable, or are they widely distributed throughout visual cortex?

The biggest question in this research area is: can an animal model for studying the pattern sensitivity of visual evoked responses

be established? This is the primary problem upon which the work of this dissertation focuses. It is not surprising that there are no reports of work on this problem by others. There are no simple approaches. One must be able to prove that the visual stimulus results in a well focused patterned retinal image. The animal must be restrained and its muscle activity minimal at the time of stimulation, but the functioning of its central nervous system must not be significantly degraded by drugs.

The two preparations to be considered are (1) an animal trained to a visual fixation task such that it can be stimulated properly and drugs are not necessary for restraint, and (2) a paralyzed, unanesthetized animal that can be stimulated with a specially designed visual pattern stimulator apparatus. For both of the above cases the instruments and procedures are designed so that a human subject can be tested under the same conditions as the animals, with the major exception that a neuromuscular blocking drug need not be administered to a human subject.

Review of Related Research

Very little was known about the neural processing of visual pattern information prior to about 1950, primarily because the techniques and instruments needed to record electrical activity from single cells in the system or to record and extract low level evoked activity from the on-going activity had not been available.

The first technique which provided focused stimuli to the retina was published by Kuffler in 1953. His method for recording from single ganglion cells of the "unopened" cat eye (cornea and lens not removed)

was to insert a hollow needle through the temporal side of the cat eye and then to introduce a needle electrode through the hollow needle. By not disturbing the normal optics of the eye, it was possible to use a focused spot of light on a tangent screen to stimulate a particular spot on the retina. With this technique, Kuffler studied the receptive fields of individual retinal ganglion cells. He found these receptive fields in light adapted animals to be approximately circular areas which, with the stimulus spot placed in a central region, caused the cell to respond with increased or decreased firing. Placing the spot in a peripheral portion of the field caused a response opposite to that of the central region. In other words, these receptive fields have an antagonistic center-surround structure. Since this initial work, a number of researchers have studied retinal cells. A good review of this topic has been given by Witkovsky (1971).

There is an inverse relationship between ganglion cell density and the size of the central regions of receptive fields (Rodieck and Stone, 1965). Measurements of the diameters of central regions of retinal ganglion cell receptive fields give a range of 0.5 to 8 degrees of arc for cat, and 2 minutes to several degrees of arc for rhesus monkey. The functional organization of these receptive fields is very dependent on the adaptation state of the eye. Under dark adapted conditions, the effect of a stimulus spot on the peripheral part of the receptive field is greatly weakened or absent, and the effective size of the central region of the field is increased (Kuffler, 1953).

By recording from single retinal ganglion cells of cat, it

has been shown that cells at this level are very sensitive to the quality of focus of the retinal image (Hill and Ikeda, 1971; Ikeda and Wright, 1971). In the area centralis, slightly defocusing the image (± 2 diopters) of the spot used to stimulate the central region of the receptive field resulted in loss of responsiveness of the cell. The axons of retinal ganglion cells form the optic nerve and proceed primarily to the lateral geniculate nucleus (LGN). Single unit activity of cells of the LGN has been recorded and analyzed in various ways. In cat and monkey, these cells have been found to have receptive fields which are in many ways similar to those of ganglion cells. The fields are approximately circular, have antagonistic center and surround regions, are not sensitive to direction of motion of a stimulus, etc. They differ from those of ganglion cells in that the central region is, on the average, smaller (Poggio et al., 1969). Hubel and Wiesel (1961) have published evidence "that the surround mechanism has a considerably stronger effect in opposing the activity evoked by stimulation of the receptive-field center in the case of the geniculate neurons as compared with optic tract units."

Also, geniculate cells are the first in this system where binocular interaction occurs , and where general brain activity governing excitability influences the processing of visual information (Angel et al., 1965; Pecci-Saevedra, 1965). Working in cat, Poggio et al. (1969) and Baker et al. (1969) investigated the time course of excitatory response of geniculate cells. Poggio et al. found the size of geniculate cell field centers to range from 0.3 to 4.5 degrees.

One might ask, do these cells with antagonistic, concentric center-surround type fields respond if the whole field is illuminated with a brief flash of light? The answer here is yes. Although there is an antagonistic center-surround relationship, the response is not completely negated. Both ganglion cells and geniculate cells do, in general, show a change from their spontaneous rate of firing in this case.

In addition to investigations of receptive field organization for LGN cells, studies have been made to determine their responsiveness to stimuli with definite spatial frequencies. Using moving sinusoidal gratings displayed on a cathode-ray tube, cells in the cat LGN were found to respond in the range 0.2 - 2.5 cycles/degree visual angle. For the squirrel monkey, this range was 0.5 - 8 cycles/degree (Campbell et al., 1969).

From the lateral geniculate nucleus, axons which are normally referred to as the geniculo-striate fibers, pass via the optic radiations to visual cortex. Three distinct areas of visual cortex have been identified anatomically and neurophysiologically. Broadmann's area 17, the striate cortex, receives the majority of the geniculocortical fibers. Areas 18 and 19 are the extrastriate cortex. They receive afferent fibers from area 17, the LGN, and a variety of other sources in both hemispheres.

In a series of papers, Hubel and Wiesel have described the receptive fields and response characteristics of visual cortex cells in areas 17, 18, and 19 of cat and monkey (Hubel and Wiesel, 1959; 1965; 1968). Their acute experiments were conducted with paralyzed,

lightly anesthetized animals, and they found it possible to classify most of the cells which they recorded into one of three categories which they defined; simple, complex, or hypercomplex. For complete definitions of these categories, it is best to refer to the original paper (1965), but even the cells classified as simple show a more complicated characteristic behavior than that of most ganglion cells and geniculate cells. They found simple cells only in area 17. Area 18 contained mostly complex cells according to their sampling, and in area 19 approximately 50 percent of the cells recorded were classified as complex. Receptive fields of cells in the cortex are rarely circular, usually elongated or rectangular. These cells are sensitive to shape, size, orientation, intensity, contrast, motion, direction of motion, and, to varying extents, location in the visual field of a light stimulus. There is evidence that cortical cells in these areas are organized in columns perpendicular to the cortical surface. Each column contains cells which respond to the same location in the visual field, but having slightly different specificities for orientation, shape, size, etc. Such an arrangement would permit efficient interconnection of simple cells to a complex cell, and complex cells to hypercomplex. Of course, establishing a classification system with three categories may well be artifical, in that there may actually be a continuum of complexities of cell characteristics.

Since cells of the nervous system have in some cases been known to behave differently under the influence of anesthetics and other drugs than they do in alert, undrugged animals, it was logical and necessary to attempt to verify the results from preparations of

the type Hubel and Wiesel used by designing an experiment to determine the properties of cortical cells using alert, behaving, completely undrugged animals. Wurtz (1969 a, b, c) carried out such experiments with rhesus monkeys trained to a visual fixation task. His work includes looking at the correlation between a cell's sensitivity to motion of a stimulus and its rate of adaptation to a stationary stimulus and finds that some units give a "vigorous and largely nonadapting response to a stationary stimulus" of proper orientation and are not affected by motion while other units adapt rapidly to a stationary stimulus but are very sensitive to motion. With regard to the shape, etc. of the receptive fields, he concludes that "the basic organization of the simpler types of receptive fields of striate cortex neurons reported for the paralyzed and anesthetized cat and monkey is found also in the awake monkey."

The angular selectivity of single visual cortex cells of paralyzed, anesthetized cats has been studied by Campbell et al. (1968) using moving square wave gratings displayed on a cathode-ray tube. Along with other criteria, the authors in general considered orientation specific units to be cortical and orientation non-specific units to be geniculo-cortical fibers. For cortical cells, they found that "the distribution of preferred angles did not show any difference between the oblique orientations and the vertical and horizontal orientations."

The basic units from which the visual system is formed are the cells. The form of this system, though its internal workings are still

fairly well concealed, can be seen at least in outline. On the average, retinal receptor cells out-number retinal ganglion cells by at least 100 to 1 in human. The number of cells in lateral geniculate nucleus is approximately equal to the number of optic nerve fibers which enter the nucleus. And, the cells of striate cortex, let alone extrastriate cortex, number at least one hundred times the cells of LGN. Thus, it can be seen that there is considerable "convergence" and information processing within the retina, some processing which is not very costly in terms of the size of the system required at the level of LGN, and a very large number of neurons in the organized structure of the striate cortex.

Retinal ganglion cells are third order cells in the visual afferent pathway which starts at the receptor cells. It is known that receptors contain a photopigment in their outer segments; but the process by which absorption of the photons results in excitation of a receptor, and eventually an active response of the second order cells, bipolar and horizontal cells, is not understood. Apparently, the meaningful activity of the first and second order cells of the retina is all in terms of slow potentials because there is no significant evidence of impluse generation by any retinal cells other than ganglion cells.

Although the studies of the electrophysiological characteristics of cells at the various levels of the primary visual pathway which have been reviewed were all carried out by observing impulse responses, activities other than impluses (frequency content 0 to less than 1000 Hz) can be recorded at each level in the system. Neural impulses are

the coded form for transmission of information along axonal fibers across distance, but transactions between cells require the exchange of a chemical transmitter substance and their outcome is determined by the weighted summation of post-synaptic potentials from all inputs onto the cell which is receiving information, as seen at the axon hillock. These timewise variations in cellular membrane potentials and electric fields of volleys of activity in fiber tracts (slow compared to the time course of single impulses) compose the slow potentials.

Slow potentials recorded in response to brief sensory or electrical stimulation are commonly called evoked responses. This term is not highly specific. For the purposes of this dissertation, it shall refer primarily to transient electrical responses which have fairly characteristic waveforms dependent upon the properties of the stimulus, location recorded from, state of arousal of the animal, and, to some extent, the individual animal.

Why are slow potentials or evoked responses of interest to one who is studying the visual system? A brief look at the number of channels into and out of the lateral geniculate (approximately 1 million) and the tremendous convergence and divergence present at points, along with psychophysical phenomena, should convince one that parallel processing of information is very important in this system. In order to understand such a system, it is necessary to determine what is the relationship of an individual unit to the local population, and to the overall population. Slow potentials and evoked responses should be valuable in this respect because they contain information primarily related to a population, the size of which depends upon the

recording conditions. For at least the following reasons, models of the visual system mechanism for processing spatial pattern information should be based on more than data from microanatomical and single unit studies. There are no techniques for simultaneously studying impulses from more than two or three cells out of a very small functionally related group of cells (Glaser, 1971). In addition, there is no guarantee that all neurons in geniculate or cortex are capable of generating impulses, and single units are usually selected for study because acceptable impulses can be recorded from them. Also, single unit studies are admitted to be biased against the smaller cells in a population.

What work has been done relative to evoked responses to diffuse and patterned visual stimuli and their relationship to anatomy and single unit activity?

Because slow potential activity recorded in response to a sensory stimulus on an EEG-type record is the combination of on-going background activity and stimulus related activity, and because the background activity is often the larger of the two, it was very difficult to study the stimulus related activity until Dawson (1954) published his photographic superposition technique for extracting this stimulus related activity. By 1961, a special purpose averaging computer had been developed to perform this extraction process (Clark, 1961). Given tools to work with, researchers began to look at sensory evoked responses.

The first paper concerned with both diffuse and patterned stimuli came in 1965 (Spehlmann). In 1967, a paper by Rietveld et al. addressed this topic in greater detail. Recording differentially from an electrode

on the scalp 1½ cm above the inion and on the midline with reference to an electrode on an earlobe, they compared the responses of 8 dark adapted human subjects to diffuse and checkerboard patterned light flashes of 2 microsecond duration. This study includes experiments to determine the effect of the size of squares in the black and white checkerboard pattern, the effect of flash intensity, the contribution of central and peripheral retina to the pattern response, and the comparison of responses to checkerboard patterns with those to line gratings and diamond patterns. The results show that for most human subjects checkerboard patterns containing squares of 10 to 60 minutes of arc (visual angle) width evoke responses that are larger in amplitude and noticeably different in waveform than responses to diffuse flashes from which the same light flux enters the eye. Checkerboard pattern responses fall into a continuum with respect to pattern size, with the largest, most distinct pattern responses being generated by patterns with approximately 12 to 15 minute squares while responses to patterns with larger or smaller features are smaller in amplitude and their waveforms become indistinguishable from diffuse flash responses as pattern features reach extreme sizes. Responses to patterns of diamonds are approximately the same as to checkerboards. Line gratings evoke responses which are different in waveshape than, and intermediate in amplitude to those for diffuse or checkerboard patterns. For patterned stimuli the response amplitude is proportional to the contrast of the pattern presented. A pattern of 20 minute squares produces much larger responses when presented to the fovea than when presented to the peripheral retina. There is no data on this point

for other pattern sizes.

Another report, Harter and White (1968), describes research which utilized diffuse and checkerboard patterned flashes to look at the effect of defocusing the patterned flashes upon the evoked responses of human subjects. The findings of this experiment were that defocusing by ± 3 diopters effectively made the responses to a pattern of 12 minute squares indistinguishable from responses to a diffuse flash, but that a larger amount of defocusing was necessary to degrade responses to patterns of larger squares by the same amount.

A study of the binocular addition of visual responses evoked by dichoptic presentation of diffuse and patterned stimuli has been done by Ciganek (1971). It was found that the response to stimulation of one eye with a white field or a large (4.5 degrees) checkerboard pattern was suppressed by the simultaneous stimulation of the other eye with a small (1 degree) checkerboard pattern.

Very recent publications by Jeffreys (1968, 1970) discuss responses he has obtained from scalp electrodes on human subjects by stimulating specific regions of the visual field with checkerboard patterned stimuli, and what he thinks these responses indicate about the locations of the source regions within the cortex which generate the activity seen as the significant peaks within the first 200 milliseconds of the response. Of course, it is not known how concentrated or diffuse these "source regions" might be.

To obtain evidence for spatially selective and orientationally selective "channels" in the human visual system, Campbell and Maffei (1970) have recorded a steady-state driven evoked response to

sinusoidal grating patterns which undergo 180 degrees phase reversal at a rate of 8 times per second. They found that the slope for the graphical curve of evoked response amplitude versus the log of the pattern contrast could be significantly increased by simultaneously presenting more than one spatial frequency or orientation while maintaining the same total light from the stimulus. These authors found that spatial frequencies for which "channels" of human central vision are sensitive are all above 3 cycles/degree of visual angle.

So, visual evoked potentials from human subjects are sensitive to type of visual pattern presented, size of features, orientation, contrast, and what region of the retina is stimulated. They are also effected by whether or not the subject is performing a task which directs attention toward or away from the visual stimulus (Kopell et al., 1969).

To determine the relationship of evoked responses to the anatomy and to single unit activity, animal research has been done, but it has all been done with diffuse flash stimuli. Fox and O'Brien (1965) demonstrated that the curve of probability of firing for a single cortical cell can duplicate rather well the evoked response which can be recorded from the same electrode after death of the cell. Creutzfeldt et al. (1969) published a study of simultaneously recorded surface evoked potentials and intracellular potentials from area 17 of cat in response to flash stimulation. Their findings and discussion of the relationships of cortical cell activity to evoked potentials are interesting, and, hopefully, it will someday be possible to do similar experiments with both pattern and diffuse flash stimuli.

Evoked potentials have been recorded from the scalp and cortex of unanesthetized monkeys (Hughes, 1964; Spinelli, 1967; Vaughan and Gross, 1969). In none of these experiments were the monkeys trained to a task. They were simply placed in a primate chair and faced toward the flashing stimulus. Hughes, and Vaughan and Gross were interested in the effects of visual system lesions. Spinelli had used simple patterned stimuli, but showed no significant effect.

This review of literature, although it has been selective, hopefully does help to point out the situation at this time. Research to determine what spatial features in the visual field cells at different levels in the visual system respond to has been done in animal experiments by single unit recording of impulses. Other investigations, which look at the responses of populations of neurons to patterned visual stimuli, have been done only with human subjects.

EXPERIMENTAL METHODS AND PROCEDURES

Basic Considerations

A primary requisite to studying responses of an animal or human subject to spatially patterned visual stimuli is a means of producing a retinal image of as high a quality as the optics of the given eye will permit. In general, there are two possible approaches to satisfying this condition which do not constrain the possible stimuli to particular geometric forms (such as interference patterns) or colors. The first possible approach is to obtain the cooperation of the animal (or human subject) in fixating and focusing upon a pattern within the visual field. The second approach is to maintain the eye in a fixed position and project the desired pattern directly onto the retina. The two groups of experiments described in this work relate to these two approaches.

A corequisite of the need to produce a well focused retinal image is that of acquiring an excellent quality original or master copy of the pattern to be used. With human subjects, the most effective patterned stimulus yet described, in terms of response amplitude and extent of waveform change, is a checkerboard pattern composed of squares having a side length of 10 to 15 minutes of arc of visual angle. To produce a master checkerboard pattern, a two layer paper assembly, one black sheet adhered on top of a white sheet with wax, was lightly criss-crossed with a scalpel blade and every other black

square lifted off. From this master pattern several series of photographic transparencies were produced, each transparency in a series containing a different number of squares.

To produce stimulation of a human subject or animal, a flash of light was projected through one of these transparencies in an appropriate projection system. Since half of the squares are transparent and half of them are approximately opaque black, the light transmitted by such a pattern is equal to ((light of the flash - surface reflection) x ½ - (loss due to the optical density of the film base)). The optical density of the "opaque" features in these patterns is slightly greater than 3.0 log units.

To produce nonpatterned stimulation which delivers the same quantity of light to the retina, a "diffuse" pattern which is a piece of clear film base plus a 0.3 log unit neutral density gelatin filter has been assembled. By use of diffuse and patterned stimuli which provided equal energy to the retina, it was expected that responses to stimulation with a diffuse pattern, a pattern of features too small to be resolved by the subject, or a completely defocused pattern should be the same.

An additional constraint imposed by the author upon the design of these experiments was that insofar as practical the apparatus to deliver the stimulus flashes to animals was designed to work equally well with human subjects. This allowed (1) recording of responses from human subjects which can be compared with published data, and (2) recording of animal responses which can, to some extent, be compared

to human responses.

Experiments with Behaving Animals and Human Subjects

When one wishes to study activity of the nervous system, experiments with behaving animals have some distinct advantages over other types of experimental procedures. Two of these are that (1) the experiments can be completely free from the effects of drugs and (2) that a large amount of data can be collected from each animal. The disadvantage of such experiments is the relatively large investment which must be made for each animal and the resulting limitation on the number of animals which can be studied.

Because of the similarity of its retina and the remainder of its visual system to that of human, a rhesus monkey (Macaca mulatta) was chosen for this experiment. In addition, since the human evoked response indicates that patterned stimulation is most effective when presented to the macular region of the retina, and this is the region of highest cone density, it is possible that a primate having a higher cone density throughout the retina than either human or rhesus would show an exaggerated example of sensitivity to patterned stimulation. Therefore, a behaving sootie mangabey (Cercocebus torquatus) was chosen as a second animal to be studied with this procedure (Kolmer, 1930). The animals used were (1) a young adult female rhesus and (2) a young adult female sootie mangabey. Neither had previously been in a primate chair.

The rhesus had never been behaviorally trained. She was 6 years old and weighed 13 lb 14 oz (6.3 Kg) before training started.

Ophthalmoscopic examination, measurement of intraocular pressures, and retinoscopy showed her eyes to be normal with less than ½ diopter spherical myopic error each. The mangabey was approximately 6 years old and weighed 13 lb 0 oz (5.9 Kg). She had previously been trained to a behavioral task. An eye examination, as above, showed her eyes to be normal except for 2 diopters spherical myopic error in each.

These animals were kept in individual cages and, by the method of Glassman et al., 1969, were transferred to a primate chair daily for training or recording sessions. Free food was supplied in the cages, but water was provided only while an animal was in the chair. At the beginning of every training session, the animal was weighed.

To obtain visual evoked response data from these animals, a visual fixation task (Wurtz, 1969a) was designed. For training and testing the animals, a programmable logic system to control the behavioral task and an acoustic chamber (IAC model AC-5) with a ground glass projection screen window in one wall were available. A ceiling light illuminated the inside of the chamber. The luminance of the white chamber wall around the projection screen was 5 to 10 candela/square meter and that of the screen itself was 1.1 candela/square meter. Two 35 mm slide projectors with solenoid operated shutters projected through a light-tight tunnel onto the projection screen. A cummulative recorder and a bank of decimal counters were available to monitor performance. Using these facilities, the final task was designed and then the several stages of training necessary to train the animal up to the final program were created (see Appendix I).

The specific purpose of the final task was to obtain the cooperation of the animal in sitting quietly, fixating and focusing upon a small spot of light in the center of the projection screen for a period during each trial when a stimulus flash might or might not be presented. The task devised required the animal to operate a single manipulandum with its hand. The animal received two types of cues, audible and visual, and was rewarded for a correct trial by a sip of water. For a correct trial the sequence of events was as follows: When no audible or visual cues were being given, the animal was allowed to pull and hold the manipulandum lever. Upon pulling the lever, a small spot of light (the fixation light) was projected on the center of the screen and remained there for a period controlled by a variable interval timing system. If the animal held the manipulandum and then released it within a short time after the offset of the fixation light (the reward period), then a tone which signified a correct response and indicated the duration of the intertrial interval was turned on and after a brief delay the sip of water was delivered. When the intertrial interval ended, after 10 or 15 seconds, the animal was permitted to start a new trial. Within such a trial a stimulus flash which covered the whole projection window was sometimes delivered. The flash was semirandomly positioned within the fixation light period. A stimulus flash of 600 msec duration was used because the system was not able to produce very brief flashes. The response recorded was that to the onset of the flash (Harter, 1971). Use of a limited hold procedure (Moody, 1970) assured that the animal must watch the fixation light very carefully in order to consistently complete trials correctly.

As a penalty for an incorrect response, a time-out accompanied by a warbling audible error signal was imposed. The basic time-out period was of fixed duration, but could be restarted during the time-out period if the animal operated the manipulandum. An incorrect trial occurred when the animal released the manipulandum before the offset of the fixation light or too long afterwards, or pulled the manipulandum during the intertrial interval.

Normal durations for the time periods in the task were: fixation light period was variable with a uniform probability density distribution over the range 1½ seconds to 8 seconds, reward period was 500 milliseconds, intertrial interval was 10 seconds, and a time-out was approximately 30 seconds.

To prevent any possibility that sounds from the system outside the acoustic chamber might be used by the animal as cues, audio white noise up to 50 KHz was produced at a moderate sound level inside the chamber.

The rhesus monkey was trained from adapting to the primate chair to performing the final task well in a period of 5 months, training 6 days per week. Figure 1 shows this monkey while she was performing the task. The animal was always provided a measured amount of water on days when training sessions were not conducted. Using the same procedures, the mangabey required more than one year to train.

For recording, a small region of the scalp over striate cortex just anterior to the nuchal ridge and approximately 2 cm from the midline was locally anesthetized with xylocaine and a wound clip with a recording lead was attached to the scalp at this location, which

Figure 1. Rhesus monkey performing the visual fixation task. The monkey is seated in a primate chair, viewing the projection screen window in the chamber wall, and operating the manipulandum with one hand. Her mouth is not far from the drinking tube through which sips of water were issued as rewards for correct completion of trials.

is within 2 degrees of the cortical representation of the fovea. This served as the active electrode. For differential recording, the indifferent electrodes were a pair of ear clips tied together through equal resistances. These electrodes were worn by the animal for several training sessions before an actual attempt to record responses was made.

During the programming and testing of the behavioral task, several humans performed the task under the same conditions which the animals were later to encounter except that the water reward was not issued. When development of the system was complete, responses to diffuse and patterned visual stimuli were recorded from several subjects. For differential recording, the active electrode was placed on the scalp using electrode paste at 1.5 cm above the inion on the midline and an ear clip was used as the indifferent electrode.

The recording equipment used included a special low-noise differential input preamplifier (similar to Schuler et al., 1966) with a fixed gain of 80, followed by another amplifier with adjustable gain and usually set to 150. Both amplifiers were designed and constructed by the author, and had a bandwidth of 0.1 Hz to greater than 30 KHz, 3 db. The amplified signal was FM tape recorded (0.1 to 1000 Hz) and a sync pulse was recorded on the same tape on a direct record channel. Recordings were played into a Fabritek model 1052 averaging computer. Individual responses could also be examined by displaying them on the computer. Averaged and individual responses were printed from the computer by a strip-chart recorder.

Experiments Using the Maxwellian View Pattern Stimulator

Stimulator and Optics

To study the evoke[d] [re]sponses of paralyzed animals to spatially patterned visual stimulation, one could refract an animal and then present the patterned visual stimulus on a tangent screen in front of the animal. A superior technique, however, is to refract the animal, then project the spatially patterned visual stimulus directly on the retina, and simultaneously view the retinal image and focus it for maximum sharpness. This is the technique which has been developed and utilized in this dissertation. It permits the experimenter to know exactly what region of the retina is being stimulated and be confident that in each experiment the image of the stimulus pattern is well focused upon the retina. Since the visual pattern stimulator apparatus which has been used is unique, it is described here. The instrument is basically a three optical channel instrument. It consists of one ophthalmoscopic viewing channel, one Maxwellian view adaptation light channel, and one Maxwellian view patterned stimulus channel. The pattern stimulating channel is based upon a design described by Westheimer (1966). This channel is combined with the other two channels using a beam splitter in front of the eye to be stimulated. This particular pattern stimulating channel has the distinct advantage that the pattern can be continuously focused through a 5 diopter range without changing either the overall size of the retinal region being stimulated or the size of any feature in the pattern in terms of visual angle. On the other side of the coin, once a setting for optimum focus has been determined a pattern can be used as its own

control by defocusing it through several diopters and not changing the retinal region being stimulated or the size of any feature in it. Figure 2 is a photograph of the pattern stimulating instrument. The original binocular viewing apparatus has been replaced by a monocular one to improve light efficiency of the viewing channel. Another modification, which is not visible, was the addition of a cross hair with a bead at its midpoint in an image plane within the viewing tube. This provided a fixation point for human subjects and an aid to the experimenter in centering and focusing the ophthalmoscope on an animal retina. A schematic diagram of the instrument is given in figure 3.

Extensive testing of the pattern stimulating instrument has been carried out both optically and by conducting evoked response experiments with human subjects. To demonstrate that the instrument is capable of producing an excellent patterned image on the retina, a lens was placed in front of the instrument and a piece of photographic paper was then exposed by flashes through the pattern stimulating channel. The results of this test are shown in figure 4. With the same lens and white paper screen, the patterned images were photographed through the viewing channel (with eyepiece and erecting lens removed) to demonstrate the effect of the viewing channel upon the image seen by the experimenter. The results of this test are shown in figure 5. As a final demonstration of the ability of the instrument to project a patterned image upon the retina, a cat was paralyzed, fitted with a contact lens, refracted, and several patterns were projected onto its retina and photographed through the viewing channel of the instrument. Two of

Figure 2. Maxwellian view pattern stimulator. The pattern stimulating channel is contained in the case which is mounted on top of the ophthalmoscope. The lid on top of the case allows insertion of a patterned transparency, optical filter, or an occluder. A calibrated scale for the range of focus is inside the case and the knob to control pattern focus is on the side of the case not seen.

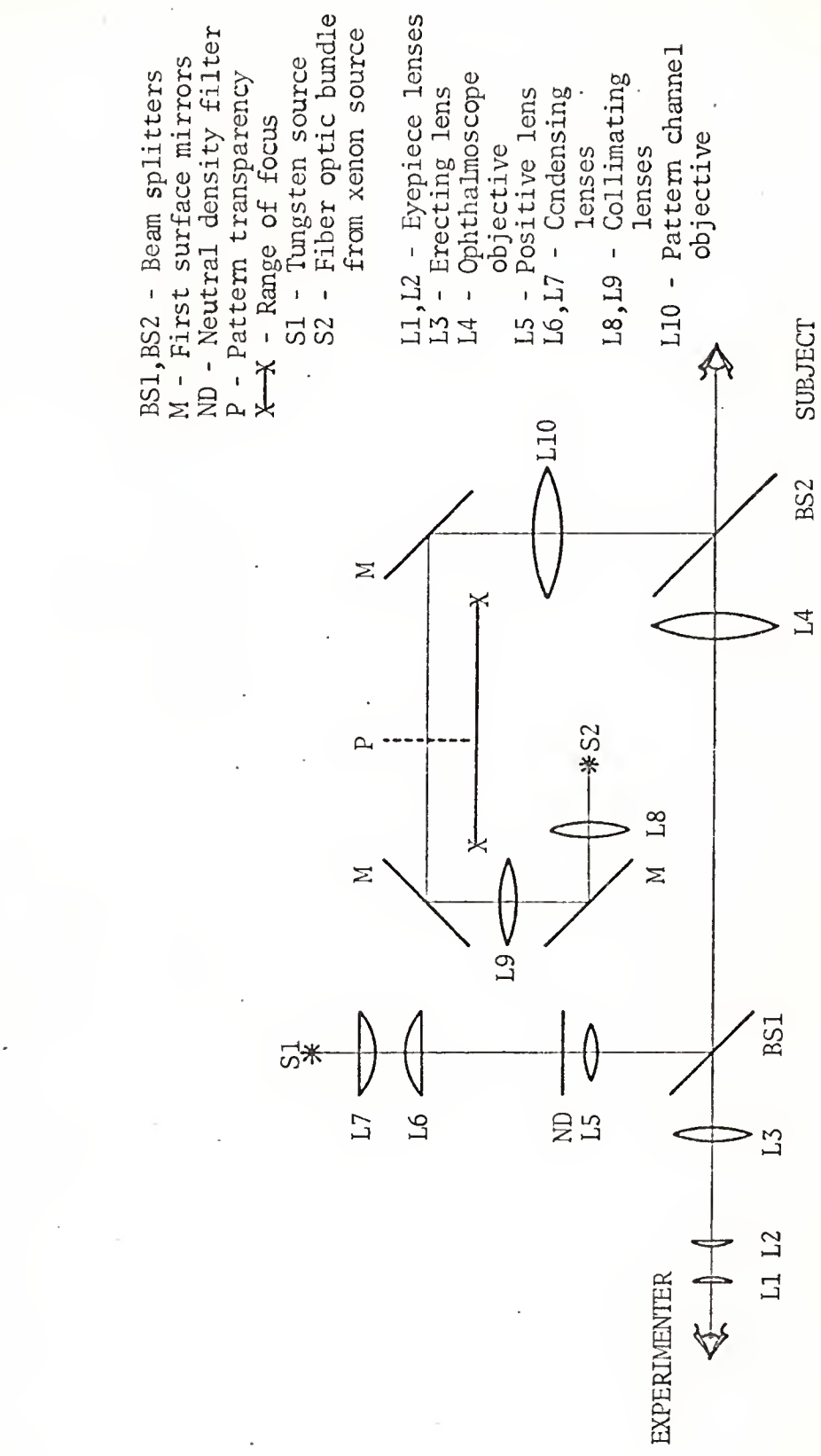
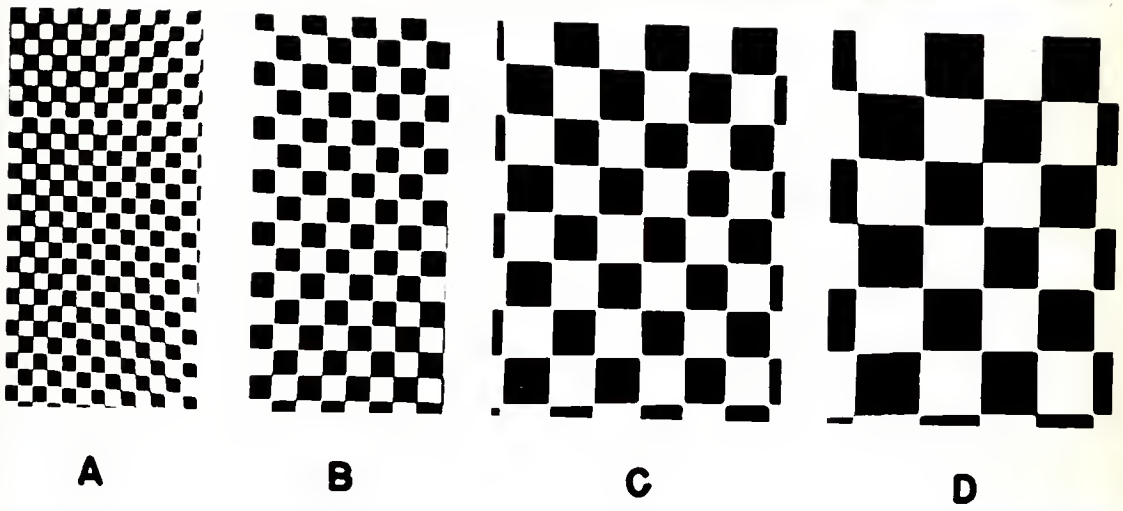


Figure 3. Schematic diagram of the Maxwellian view pattern stimulator instrument.



EXAMPLES OF THE QUALITY OF PATTERN WHICH THE PATTERN STIMULATOR INSTRUMENT IS CAPABLE OF PROJECTING.

A. 0.8 mm/sq. pattern = 17.5 min. of arc = 68 μ on the retina

B. 1.4 mm/sq. pattern = 31 min. of arc = 120 μ on the retina

C. 2.5 mm/sq. pattern = 55 min. of arc = 212 μ on the retina

D. 3.6 mm/sq. pattern = 79 min. of arc = 306 μ on the retina

Figure 4. A test of the Maxwellian view pattern stimulator: checkerboard patterns projected through a glass lens directly onto photographic paper.

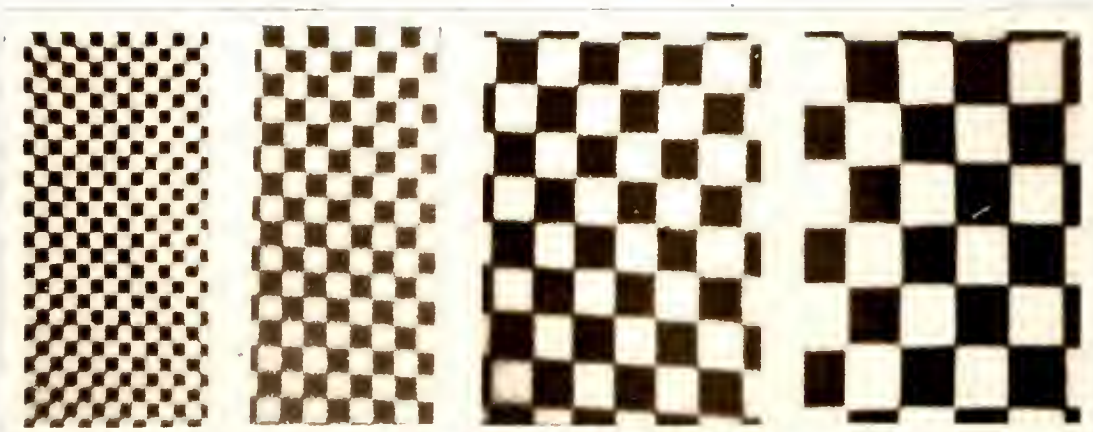


Figure 5. A test of the Maxwellian view pattern stimulator: checkerboard patterns projected through a glass lens onto a white paper screen and photographed through the viewing channel of the instrument. A modification of the original design of the viewing channel to improve light efficiency at the expense of image quality was made to allow viewing of the fundus at the standard adaptation light level chosen for use in these experiments (780 trolands retinal illumination).

these photographs are shown in figure 6.

Obviously, to study responses of a paralyzed animal to spatially patterned visual stimuli, one must have high quality contact lenses available because the surface of the cornea of a paralyzed animal dries, becomes irregular, and does not permit the projection of a high quality image onto the retina. In agreement with Vakkur et al. (1963), for cat a supply of zero diopter plastic lenses of radius 8.7 mm has served nicely. Additional correction, when necessary, was obtained by first utilizing the range of focus available in the instrument and then by placing a lens in the spectacle plane.

The patterns projected by this instrument were on transparencies that were mounted in 35 mm slide frames.

Animals and Electrode Implantation

Six cats were used in these experiments. They were all healthy adults and weighed between 2.5 and 4.3 Kg. One young adult rhesus monkey (Macaca mulatta) was used. He weighed 3.8 Kg.

The operations to place chronically implanted electrodes into these animals were conducted as follows. Ten mil insulated stainless steel wire electrodes with sharpened tips were prepared in advance. An animal was anesthetized with sodium pentobarbital (Nembutal). A surgical anesthetic level was achieved with an initial dose of 15 to 20 mg/kg administered i.v.. Additional anesthetic was given later in the procedure, if necessary. Using sterile surgical techniques, bipolar electrodes were placed in optic nerve and lateral geniculate nucleus stereotaxically while photically evoked responses were

Figure 6. The ultimate test of the Maxwellian view stimulator: checkerboard patterns projected onto the retina of a paralyzed cat and photographed through the viewing channel of the instrument. In order to be photographed, it was necessary that the light pass through the optics of the cat eye twice and the viewing channel of the instrument once. Also, it should be noted that while light entered the eye through only a portion of the cornea and pupil, the whole pupil was used in viewing the retina. Therefore, the actual retinal images were superior to the images photographed.

recorded from them to insure that the desired structure had been located. One mm diameter stainless steel ball electrodes were placed epidurally over striate and extrastriate visual cortex (Bilge et al., 1967; Daniel and Whitteridge, 1961). As an indifferent electrode, on cats a loop of stainless steel wire was mounted on top of the skull over the frontal sinus. Electrodes were held in position by fastening their shafts to the skull with a fast-setting acrylic plastic. A block of plastic into which two holes had been drilled and tapped was cemented onto the skull centered on the midline at approximately anterior 24 mm. The electrode leads were brought to a miniature electrical connector socket and this socket was mounted in a mound of plastic on top of the skull. The animal was allowed to recover from the anesthetic and returned to its cage.

Recording Sessions with Human Subjects

An effective way to test the Maxwellian view pattern stimulator instrument was to use it to record evoked responses from human subjects. Three subjects were used. They were all between 20 and 30 years old. Two were emmetropic and had not been recorded from previously. CD wore corrective lenses. An active electrode placed on the scalp at 1.5 cm above the inion on the midline and an ear clip indifferent electrode were used. A subject was placed in a well darkened electrically shielded room, given a chin rest in front of the stimulator, and asked to fixate a tiny bead at the midpoint of a vertical hairline through the center of the adaption light field. Patterns, light levels, and recording instruments were as described in the next section for animals.

Recording Sessions using Animals

In a brief sketch, during a recording session an animal was anesthetized with halothane gas anesthetic long enough to intubate it with a tracheal cannula and administer the initial dose of neuromuscular blocking drug i.v., then it was moved into an electrically shielded room, placed on a continuous infusion of neuromuscular blocking drug, respirated, refracted and corrected, allowed to adapt to a fixed background field (adaptation light), and then it was stimulated and recorded from for a period of from 6 to 8 hours. At the end of this period the animal recovered from the paralysis and was returned to its cage.

The priorities within these recording sessions were (1) to determine whether or not the visual evoked responses of cat or monkey are sensitive to spatially patterned visual stimulation and if so, then (2) the effect of pattern feature size, (3) whether or not the responses are repeatable over hours and weeks, and (4) the effect of quality focus of the pattern. In accordance with these priorities, the general plan for recording sessions was to obtain responses from the animal to diffuse flashes and to a series of 4 or 5 checkerboard patterns of different feature size, to run this series in forward and reverse pattern feature size order 2 or 3 times within one session, to run selected patterns additional times, and using the range of focus built into the stimulator, or external lenses, to compare responses to a given pattern when it was well focused and when it was defocused by different amounts.

The choice and order of averaging runs within each session was generally in agreement with the priorities stated. This project

was essentially exploratory, and therefore a rigid design or order for the collection of the responses was not appropriate.

The use of drugs was carefully limited to the minimum necessary to restrain the animal and maintain it in a good physiological state. Appendix II provides details of the use of drugs in this project. Over all sessions with cats, the average amount of gallamine triethiodide (Flaxedil) administered was 9 mg/kg/hr.

To obtain an early warning of any significant change in the operation of the animal's respiratory or cardiovascular systems, a respiration monitor and alarm system to monitor end expiratory CO_2 level was designed and developed by the author. It was used in conjunction with a Beckman LB-1 CO_2 meter. The details of this system are given in Appendix III.

To conduct a recording session after all the necessary instruments were ready, a chronically implanted animal was given an injection of atropine i.m., and received one drop of one percent cyclopentolate hydrochloride (Cyclogyl) topically applied to each cornea. After 30 minutes, halothane gas anesthetic was administered to the animal. The anesthesia was continued while respiratory and cardiac activity were watched and reflexes were tested. When proper anesthetic level was reached, the animal was intubated with a tracheal cannula (inflatable cuff type). The 23 gauge needle of a scalp infusion set which was attached to a syringe was inserted into a vein. The animal was switched from the O_2, halothane mixture to air and allowed to breath off the anesthetic as the initial dose of neuromuscular blocking drug, gallamine triethiodide, was administered slowly through the i.v. catheter.

At this point the animal was connected to a positive pressure respirator pump. The animal was wrapped with an automatically controlled heating blanket and placed on a canvas bed which has a metal frame and, on the front end, an adjustable head-holding bracket which can be screwed to the plastic block on top of the animal's head. The animal was then connected to a syringe pump. The CO_2 monitor and alarm system was now in operation, and the respirator was adjusted to give a steady 4 percent end expiratory CO_2 level. The EEG was continuously monitored with an oscilloscope. Using palpation or a stethoscope, a check on the rate and strength of the heartbeat was made frequently. Each cornea was treated topically with a steroid solution (dexamethasone), and a few minutes later a solution of methylcellulose was applied to each cornea and to the inside surface of the contact lenses. The contact lenses were placed on the eyes and examined with an ophthalmoscope to insure that the fit was acceptable and no air bubbles were trapped under the lenses. The eyelids and nictitating membrane were held open by an opaque ring cemented to the outside surface of the contact lenses. Normally the eye to be stimulated was fitted with a high quality transparent plastic lens and the other eye with an opaque black plastic lens. Next the fundus of the eye to be stimulated was then studied with a hand-held ophthalmoscope to become familiar with the pattern of blood vessels, especially, for cats, those in the neighborhood of the area centralis. Area centralis was located using the pattern of retinal vessels and the coordinates, 14.7 degrees radially from the center of the optic disc at an angle of 22 degrees above horizontal and temporal to the optic disc (Vakkur et al., 1963).

In the paralyzed animal, because the eye maintains a fixed position in the orbit, it was possible to orient the eye to be stimulated by orienting the head. Therefore, the bracket to which the animal's head was attached was adjusted to align the visual axis of this eye to a straightforward horizontal gaze.

A streak retinoscope was used to refract the eye and any corrective lens necessary was mounted in the spectacle plane on the front of the stimulator instrument. The pattern stimulator instrument was then positioned in front of the eye and aligned such that the area centralis (macular region for monkey) was in the center of the field of view, which for this instrument was approximately 30 degrees in diameter. The ophthalmoscopic viewing channel was focused and the adaptation light level adjusted. A patterned stimulus transparency was placed in the instrument and with a continuous light source temporarily attached to this channel the pattern was projected, viewed, and focused on the retina. The focus was tested with several transparencies with different feature sizes and the focus adjustments were made as many times as necessary in order for the investigator to be confident that the best possible focus had been achieved. The light source to the pattern stimulating channel was then changed from continuous to xenon flash. Figure 7 shows a cat during an actual recording session.

The standard adaptation light intensity used produced a retinal illumination of 780 trolands. A standard flash intensity was chosen. Using the diffuse pattern, the investigator when at the standard adaptation level found the standard flash intensity to be 2.5 log units above

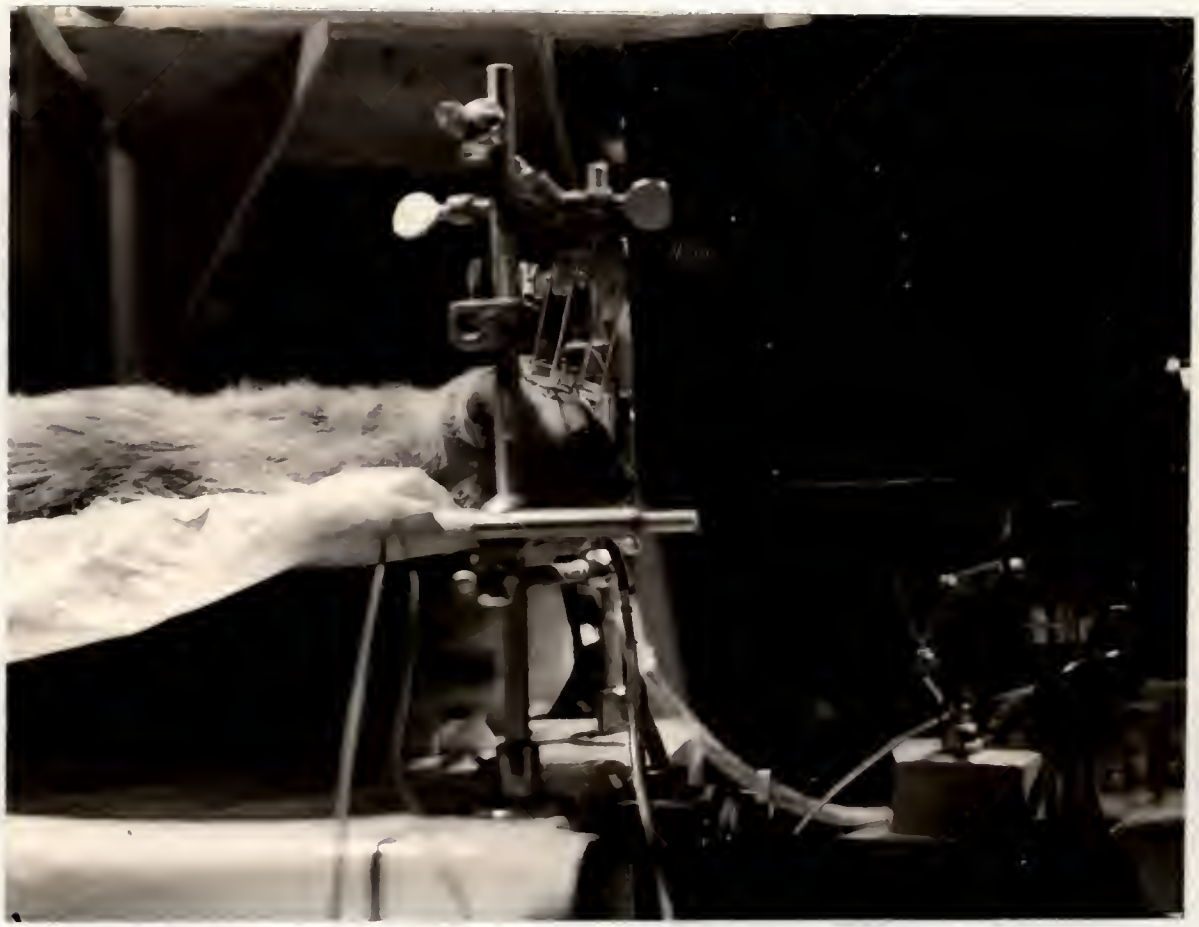


Figure 7. Photograph of an historical event: the experiment in which cortical evoked responses sensitive to spatially patterned visual stimuli were first recorded from cat. The cat is paralyzed, artificially respirated, and warmed by an automatically controlled heating blanket which has been laid aside for the photograph. Its head is supported and positioned by a plastic bracket. The animal is wearing a contact lens in its right eye and is being visually stimulated (left eye occluded). Recording is from chronically implanted electrodes.

threshold for detection of the flash.

Trigger pulses to both stimulation and recording equipment were normally spaced 2.25 seconds apart. The xenon flashes (approximately 10 μsec duration) for the stimulator were obtained from a Grass model PS2 photostimulator and conducted to the pattern stimulator through a 1/8 inch diameter fiber-optic bundle. Recording channel amplification was obtained from Tektronix type 122 differential amplifiers with (-3 db) bandwidth normally set at 0.2 to 1000 Hz. No additional filters were used during paralyzed animal experiments. The amplified individual responses were sometimes FM tape recorded simultaneously with the averaging process which was performed using a Fabritek model 1052 averaging computer.

The stimulator, respirator, infusion pump, recording equipment, and data logs were carefully attended to between runs. Appropriate action was taken if any signs of excessive wetness in the lungs or mucous in the trachea were encountered. The volume of drug remaining in the syringe pump was watched closely, and a record of the quantity of drug infused was kept. The retina was viewed periodically to insure that the position of the retinal landmarks had not changed. The time interval between averaging runs ranged from 4 to 15 minutes. Averaged responses normally contained 64 individual responses, but on occasion contained 32, 128, or 256 responses.

When all of the desired runs for a recording session had been collected (or up to 30 minutes before), the infusion was switched to glucose saline with no gallamine before the stimulator was moved away from the animal. A final check of the retinal position and corneal

transparency was made to insure that no change had occurred during the experiment, and then the contact lenses were removed. The animal was observed until a diaphragm reflex or movement of the jaw was seen, and then neostigmine was administered slowly through the i.v. catheter up to a maximum of 25 nanograms per kilogram. When the animal's ability to respirate itself was adequate, it was disconnected from the apparatus. After a period for observation, the animal was returned to its cage.

The procedure for recording from paralyzed monkey was essentially the same as that for cat with the exceptions of different drug dosages, different contact lens curvatures, and different retinal landmarks.

All animals used in these experiments survived and were healthy afterwards.

RESULTS

Human Subjects with the Behavioral Task

When given verbal instructions, human subjects were able to learn the behavioral task in a small number of trials. Two human subjects served in this experiment. The evoked responses recorded from them are shown in figure 8, and the simultaneously recorded cumulative records of their performance are shown in figure 9.

The subjects were attentive and very few errors were made. At latencies between 100 and 300 milliseconds, the response waveforms were sensitive to pattern feature size, but the waveform changes were not large. In the pattern responses of subject HD, an increase in the negativity of the peak at 120 milliseconds was the largest waveform change. For subject CD, the difference between pattern and diffuse responses is a positive-negative-positive sequence which starts at a latency of 170 milliseconds in the 15 minute of arc pattern response and translates to noticeably shorter latencies in the responses to patterns with larger feature sizes.

In this research, responses were recorded from human subjects in order to provide data for comparison of the two methods used with each other and with responses in the literature. The effectiveness of each of these methods for producing spatially patterned visual stimulation of animals should be proportional to its effectiveness with human subjects.

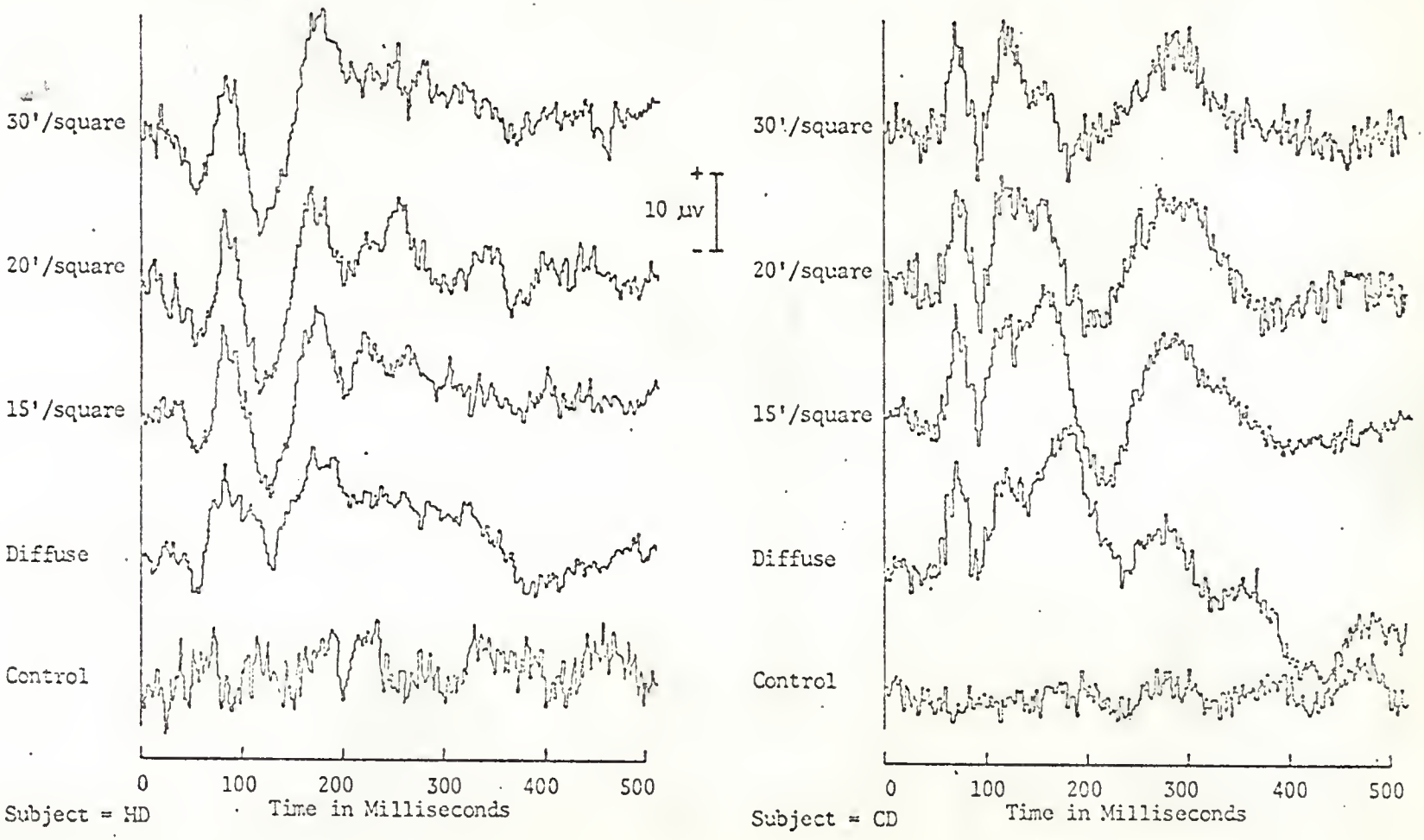
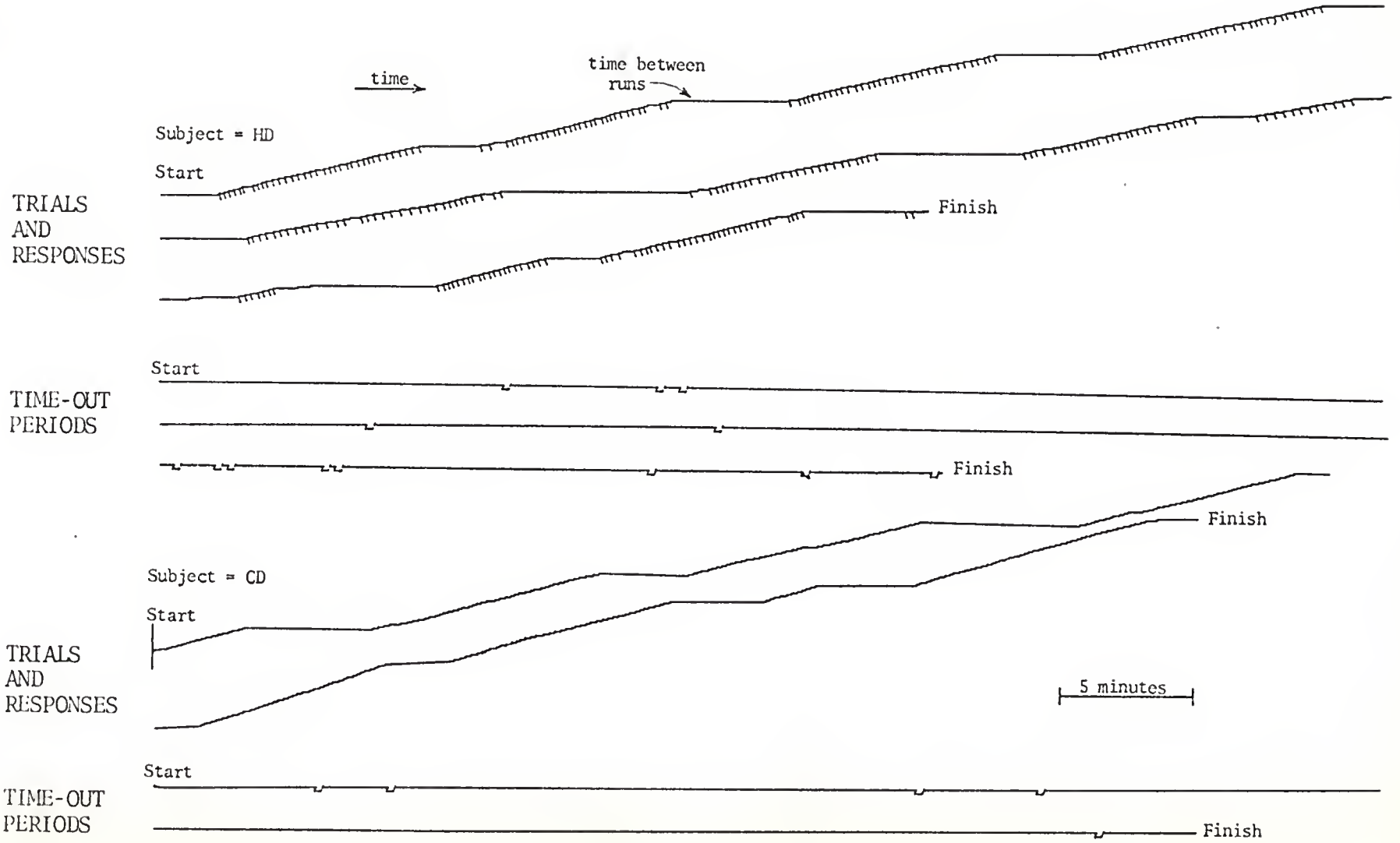


Figure 8. Human evoked responses to diffuse and checkerboard patterned stimuli using the visual fixation task. 32 individual responses/average response.

Figure 9. Cummulative records of the performance of two human subjects. In the records of trials and responses, each upward step marks the beginning of a trial. For subject HD, each downward stroke indicates the correct completion of a trial. In the records of time-out periods, the duration of the negative going pulse indicates the duration of the period.


time
time between runs
Subject = HD
Start
TRIALS AND RESPONSES
Finish
Start
TIME-OUT PERIODS
Finish
Finish
Subject = CD
Start
TRIALS AND RESPONSES
5 minutes
Start
TIME-OUT PERIODS
Finish

Monkeys with the Behavioral Task

In training, the rhesus made steady progress, especially from the point where she was given the manipulandum and discovered that it controlled the task. After 5 months of training, she was correctly completing greater than 80 percent of all trials started. At this time, fixation light periods required some lever holds up to 10 seconds and the fixation light spot was dim, usually colored (red or green) and subtended 25 minutes of arc (visual angle). For two weeks, ear clip electrodes were placed on her during training sessions. By 5½ months, 95 percent of all trials started were being completed correctly. A record of the animal's performance and the distribution of her reaction times to the offset of the fixation light is given in figure 10. Evoked responses recorded simultaneously with that performance are given in figure 11. These responses have positive peaks at 90, 130, and 150 milliseconds and a distinct negative peak at approximately 107 milliseconds. The responses to 15 and 20 minutes per square patterns are noticeably larger in amplitude than the response to diffuse flash stimulation. Pattern sizes were not repeated during that recording session. Visual comparison of the set of 32 individual responses to the 15 minute per square pattern with those to the diffuse stimulus shows that the responses to the patterned stimulus were more consistent and larger than those to the diffuse stimulus.

In several other sessions when some responses were recorded from this animal, recording procedures and electrodes were being developed and no usable sets of data were obtained. All data collection from the scalp electrode was preliminary to data that was to be

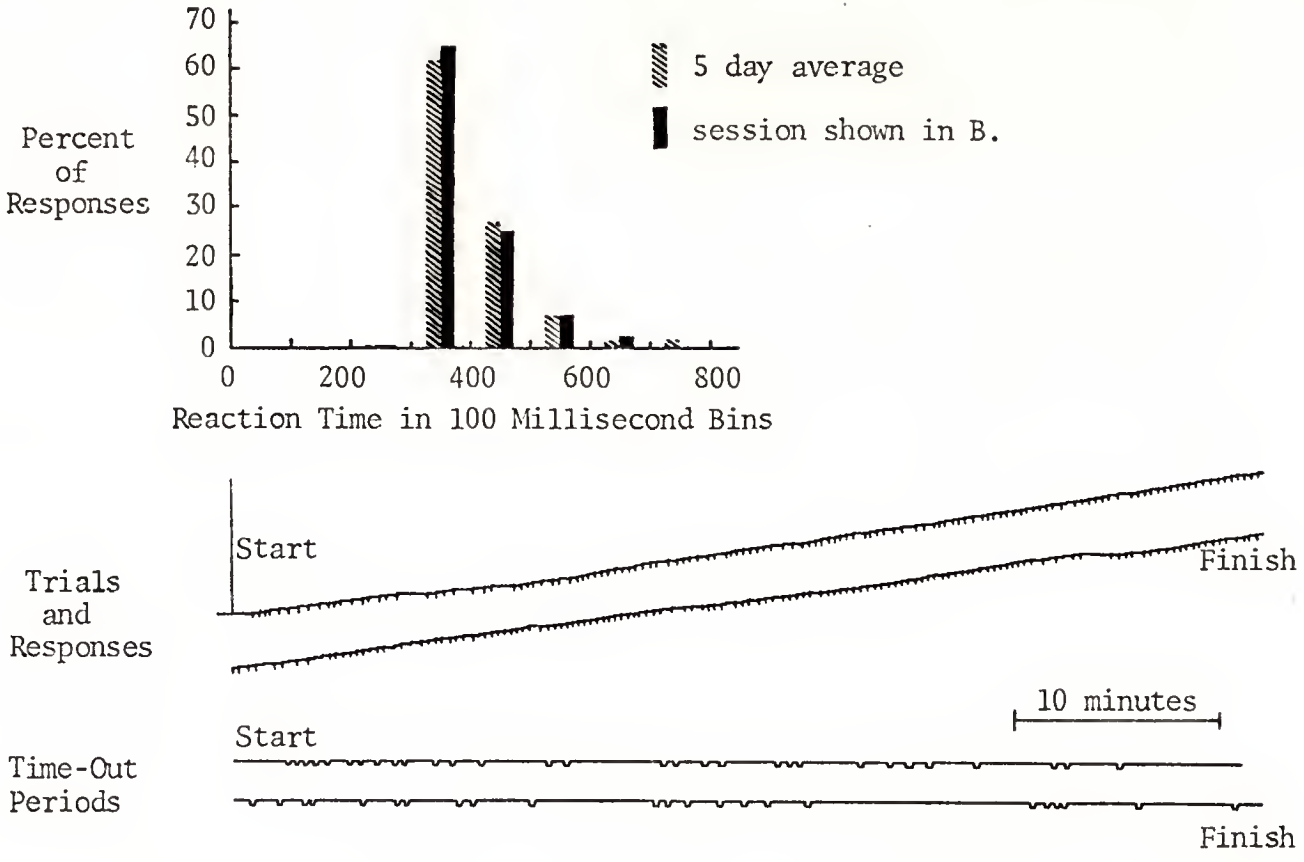


Figure 10. Histogram of reaction times and cummulative record of performance of a rhesus monkey. (A) The average is based on 5 consecutive sessions and contains the session shown in B as the 3rd session. (B) Same type record as in figure 9. Note that all but a few of the time-outs were caused by a lever pull during an intertrial interval (exceeding the speed limit) rather than an incorrect response.

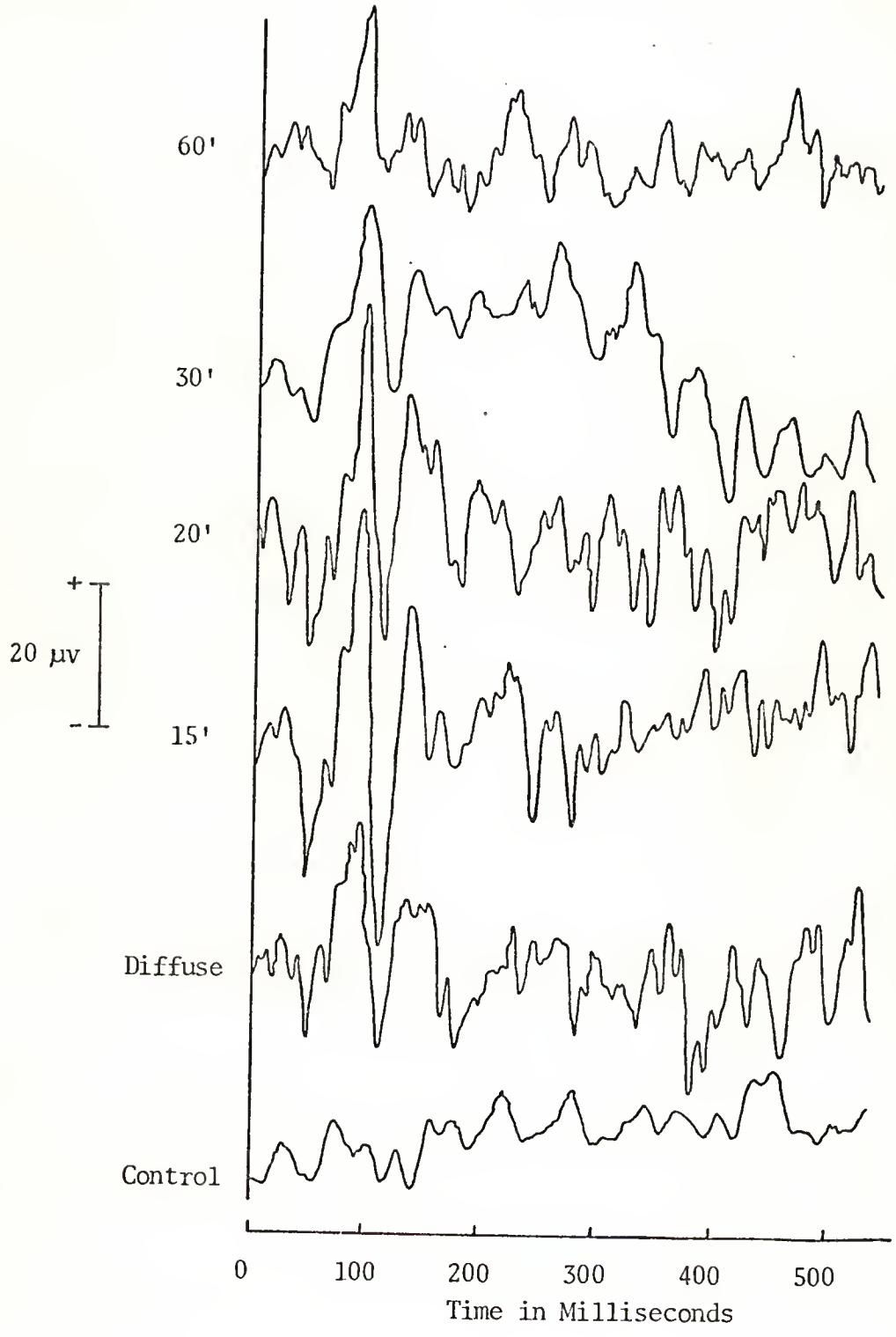


Figure 11. Evoked responses of rhesus monkey to diffuse and checkerboard patterned stimuli using the visual fixation task. 32 individual responses/average response.

recorded from an array of implanted ball type epidural electrodes over striate cortex. The implant operation was performed under sodium pentobarbital anesthesia. Near the end of the operation the veterinarian who was present administered a small additional dose of anesthetic, i.m. (phencyclidine hydrochloride (Sernylan)), and its facilitatory interaction with the pentobarbital was fatal to the animal.

The increase in amplitude of the 15 and 20 minute per square pattern responses over that of the diffuse response was interpreted as a possible indication of sensitivity of the rhesus evoked response to pattern.

The mangabey trained well until the manipulandum was introduced. From that point on, her progress was not steady. After several months of training, she knew the task well enough to perform it very well on some days, but her performance was not consistent. Her motivation to work seemed not to be very well related to deprivation or weight loss. Additional problems developed and when the rhesus died, it was decided by the author not to pursue the training of this animal further. The mangabey's training has been continued by another student, but no data has been recorded at this time.

Maxwellian View Stimulation of Humans

The visually evoked responses of three human subjects to diffuse and patterned stimuli are shown in figure 12. They demonstrate sensitivity of the human evoked response to spatially patterned stimuli. Responses from these same subjects are presented in figure 13 along with "difference waveforms" derived by subtracting from the given response

Figure 12. Responses of humans to diffuse and patterned stimuli presented by means of the Maxwellian view stimulator. Averages of 64 responses with 2.25 seconds between stimulus flashes.

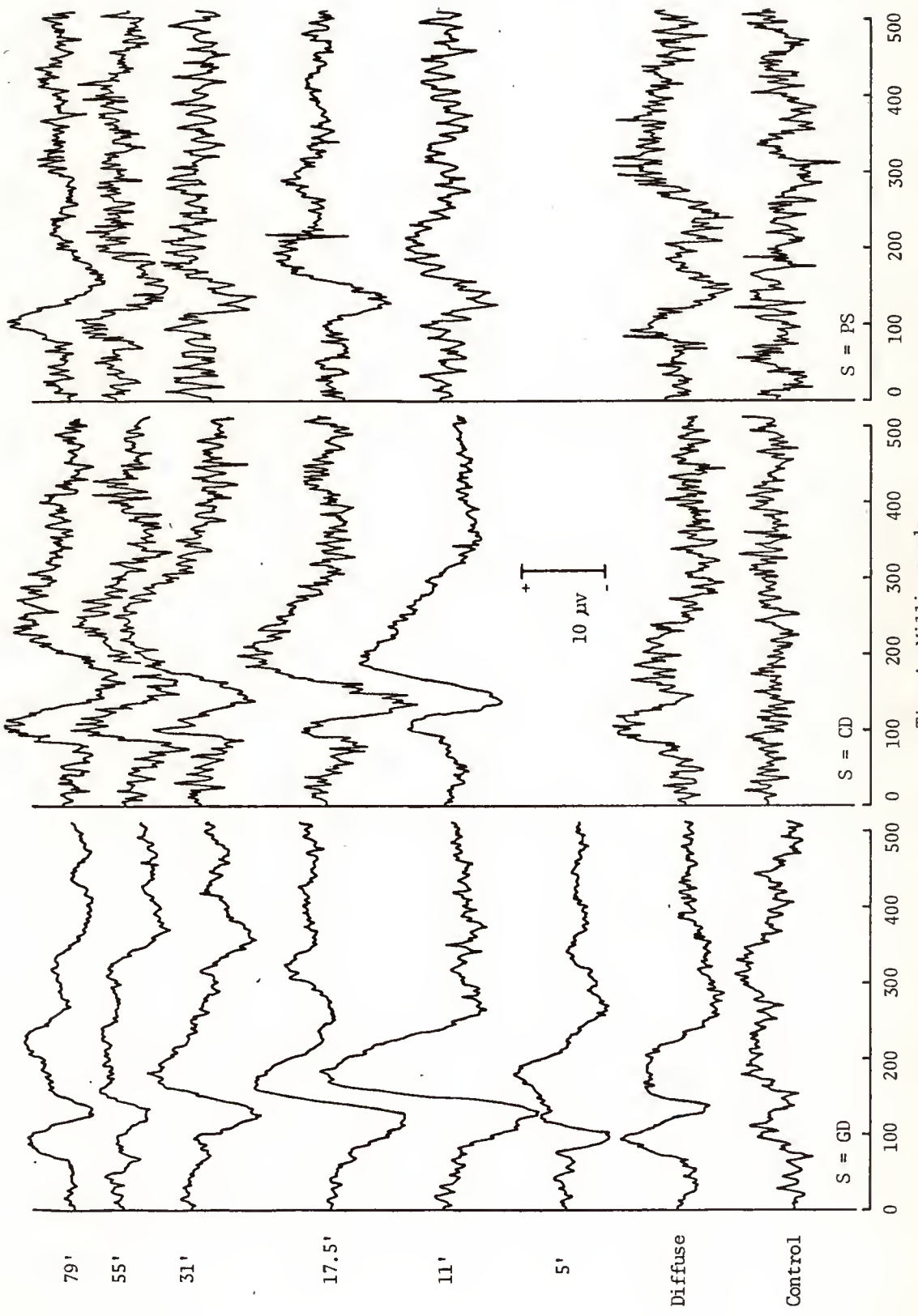
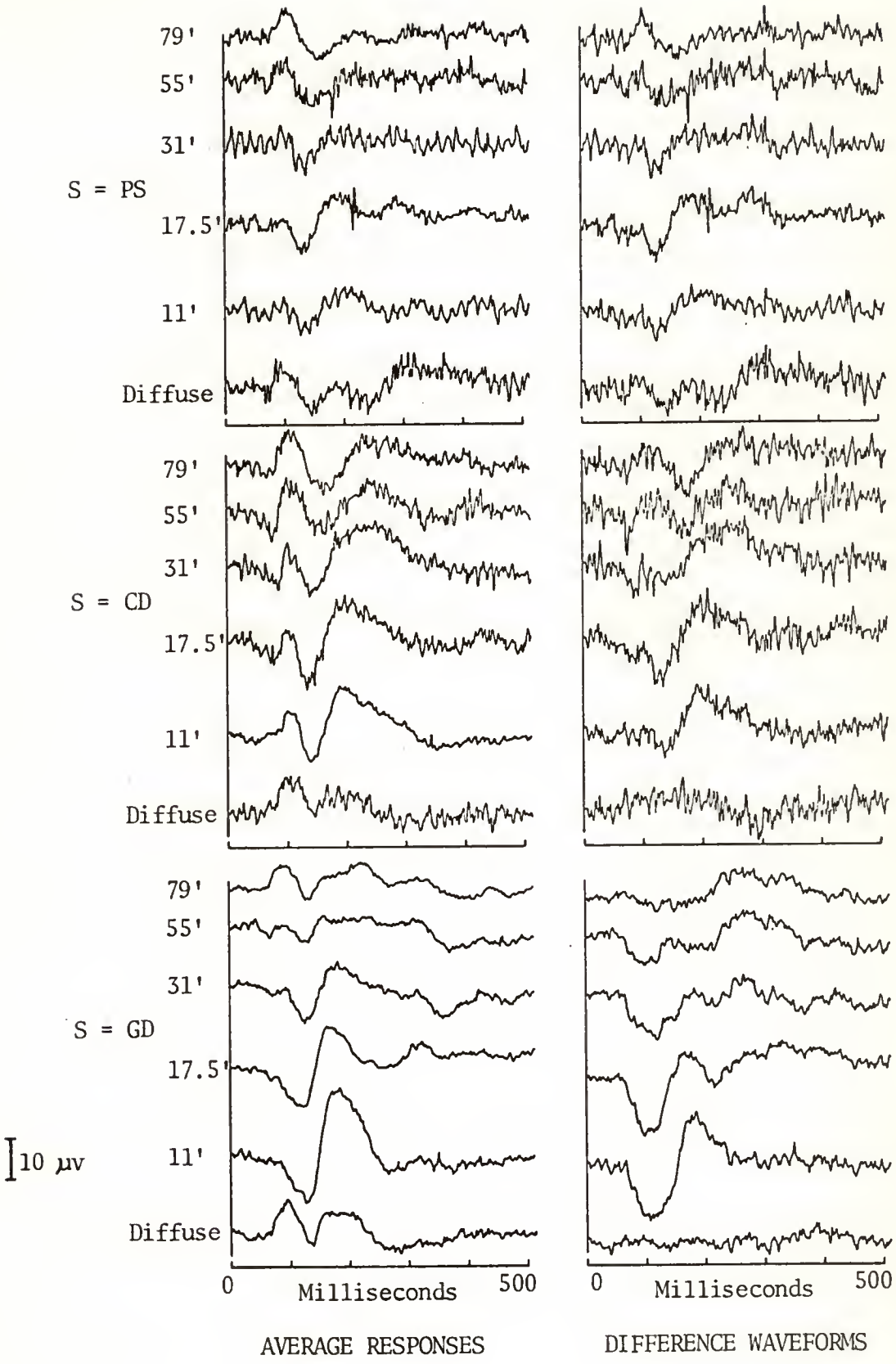

79'
55'
31'
17.5'
11'
5'
Diffuse
Control
S = GD
S = CD
S = PS
0
100
200
300
400
500
+
10 μv
-
Time in Milliseconds

Figure 13. Comparison of the responses evoked by checkerboard patterned visual stimuli and a diffuse flash stimulus which produces the same average retinal illumination. Difference waveforms (pattern response - diffuse response) are given for 3 human subjects. Stimulation was by means of the Maxwellian view stimulator.


79'
55'
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S = PS
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79'
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31'
S = CD
17.5'
11'
Diffuse
79'
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31'
S = GD
17.5'
11'
Diffuse
10 μv
0
Milliseconds
500
0
Milliseconds
500
AVERAGE RESPONSES
DIFFERENCE WAVEFORMS

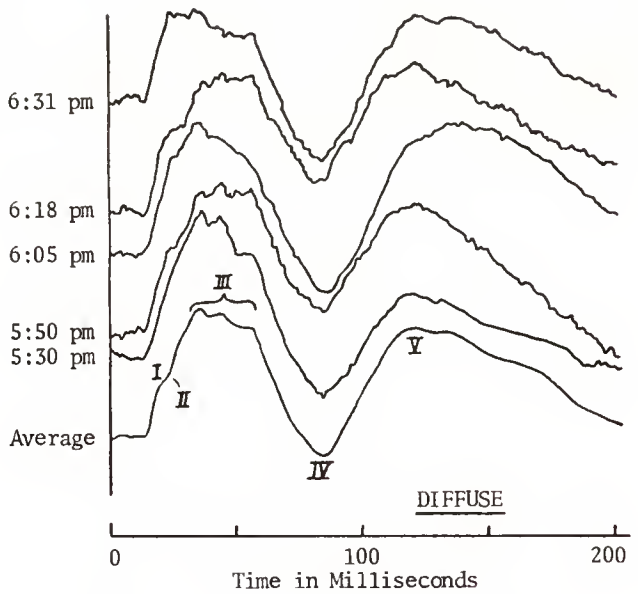
(pattern or diffuse) a diffuse response. Pattern sizes were repeated for each of these subjects and the responses were consistent. The effects of patterned stimulation relative to diffuse stimulation, and pattern feature size, as seen in these responses, are in agreement with the findings of Rietveld et al., 1967, and Harter and White, 1968.

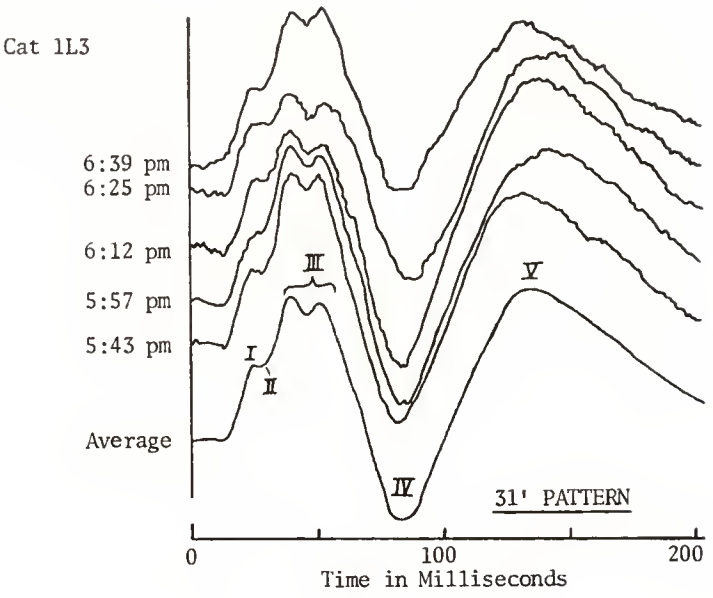
Maxwellian View Stimulation of Cats

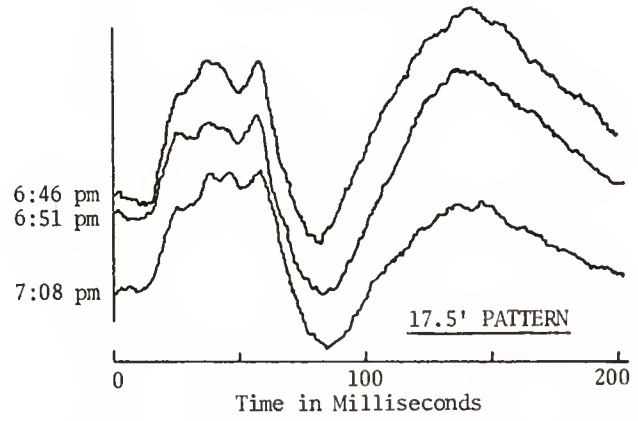
The cortical responses of the first two cats from which responses were recorded, were observed as they were averaged on line in an attempt to identify any changes in waveform which correlated with a change from diffuse to patterned stimulation or vice versa. Such changes were identified and the stimulus conditions were alternated a number of times to determine whether or not the changes were repeatable and consistent. Figure 14 shows such data for cat 1L3.

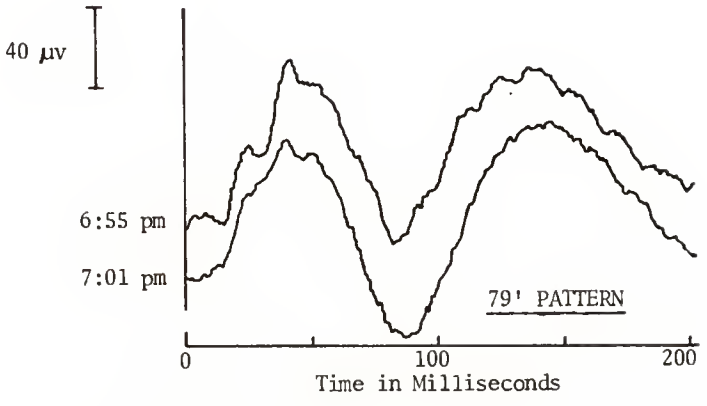
In the upper half of figure 14, average responses were recorded for a diffuse stimulus and a checkerboard patterned stimulus, alternately, over a 70 minute period, and they showed consistent waveform features in the response to pattern which were not found in the response to diffuse stimulation. To demonstrate the consistency of this data, the averages of all five average responses for the diffuse stimulus and for the 31 minute patterned stimulus are also given in figure 14. Using the terms defined by Creutzfeldt, et al., (1969) for the components of the cat cortical visual evoked response, the response to 31 minutes of arc pattern stimulation has a more distinct wave I-wave II complex, a double peaked wave III, and a larger wave IV than the response to diffuse stimulation. Also, in the lower portion of figure 14, are

Figure 14. Repeatability of cat cortical evoked responses to diffuse and patterned visual stimuli within one session. Time of run is printed along the ordinate. In the upper portion of the figure runs were alternated between the diffuse and the 31 minute pattern stimuli. An ensemble average of 5 average responses is given for each of these 2 cases. In the lower portion of this figure, responses to 2 other pattern sizes are compared. Using terms defined by Creutzfeldt et al. (1969), waves I, II, III, IV, and V are labeled on the ensemble averages. Each average response contains 64 individual responses to stimulus flashes 2.25 seconds apart.


6:31 pm
6:18 pm
6:05 pm
5:50 pm
5:30 pm
Average
I
II
III
IV
V
DIFFUSE
0
100
200
Time in Milliseconds


Cat 1L3
6:39 pm
6:25 pm
6:12 pm
5:57 pm
5:43 pm
Average
I
II
III
IV
V
31' PATTERN
0
100
200
Time in Milliseconds


6:46 pm
6:51 pm
7:08 pm
17.5' PATTERN
0
100
200
Time in Milliseconds


40 μv
6:55 pm
7:01 pm
79' PATTERN
0
100
200
Time in Milliseconds

responses to two patterns with different feature sizes obtained in an alternating series of averaging runs. It can be seen that the waveform changed with pattern feature size and that the changes were consistent with this series.

For cat 1L3, the array of different response waveforms obtained with pattern feature size is displayed along with difference waveforms (pattern minus diffuse) in figure 15. These responses were practically duplicated by responses recorded from the same animal thirteen days later and displayed in figure 16.

A series of responses to different intensities of diffuse flash were recorded. It is shown in figure 17 and is evidence that the waveforms seen with patterned stimuli are not obtained with different intensities of diffuse stimulation.

One chronically implanted optic nerve electrode was in place in cat 1L3, but was not usable in this experiment because in a preliminary recording session the cornea of the eye ipsilateral to the implanted nerve was damaged by a tight fitting contact lens. Therefore, stimulation for the data described above was to the eye contralateral to the implanted nerve.

Another animal, cat 1K9, possessed usable electrodes both in optic nerve and on cortex (epidural). Responses recorded from this animal are shown in figures 18 through 22. During the first recording session with this animal, problems with the recording equipment limited the data collection and only responses from cortex were recorded. Figure 18 shows the effect of pattern feature size. Responses from epidural striate and extrastriate electrodes were quite similar and

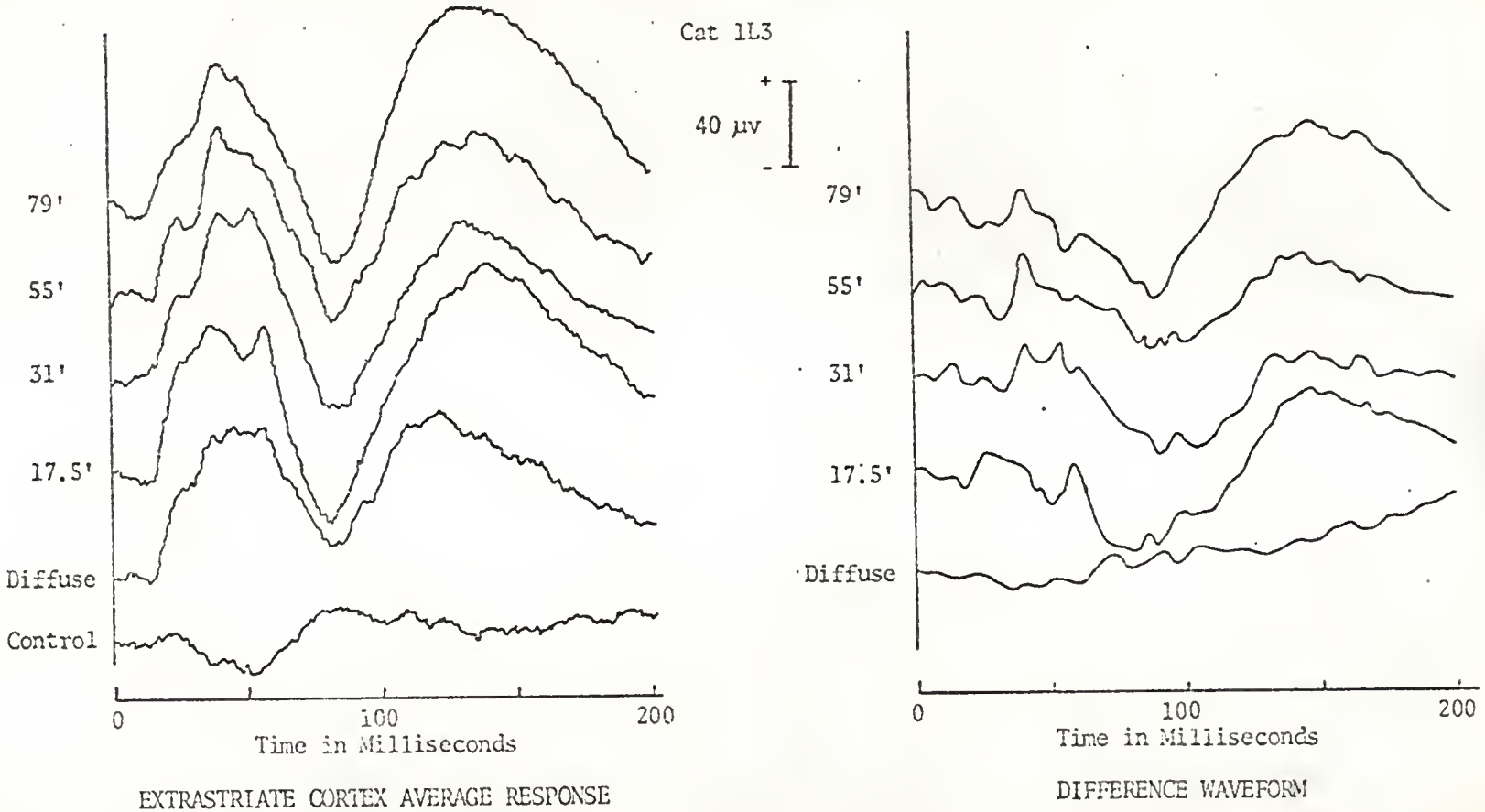


Figure 15. The effect of pattern feature size upon the cortical evoked response of cat 1L3. 64 individual responses/average response. 2.25 seconds between stimulus flashes.

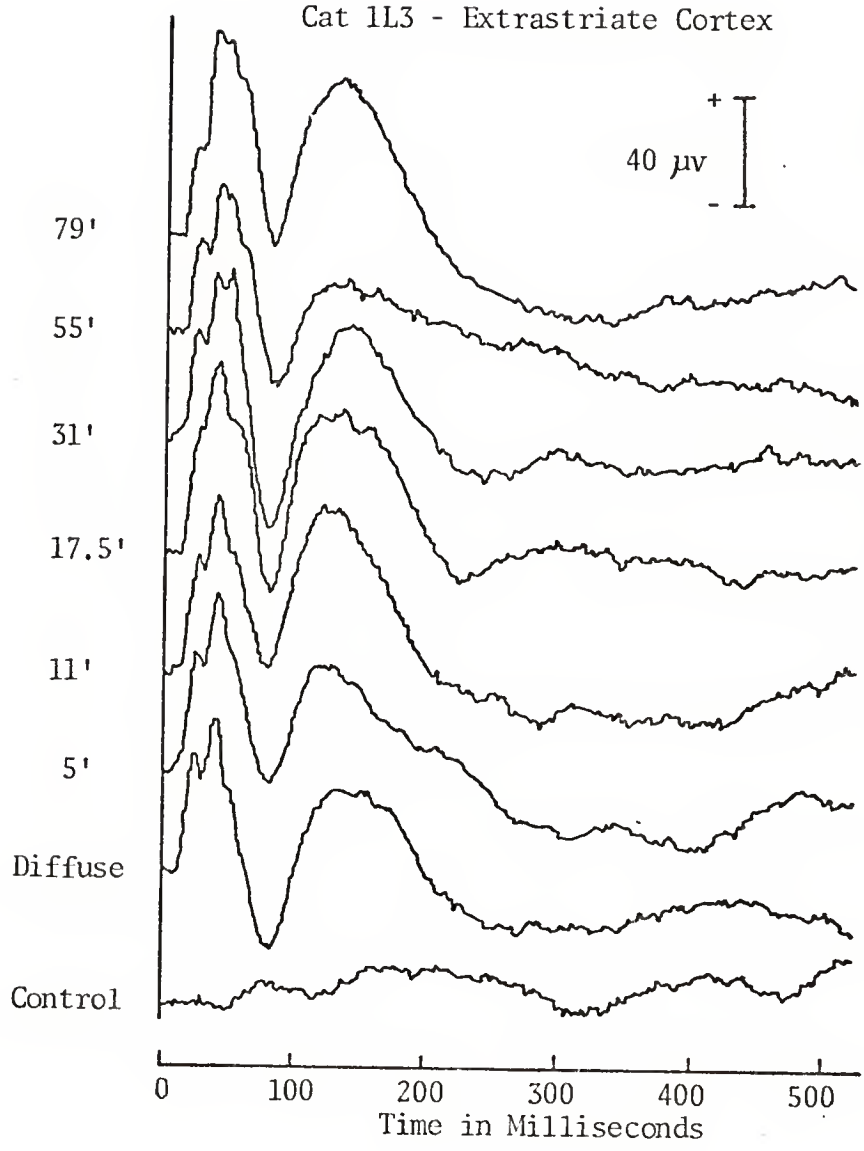


Figure 16. Repeatability of cat cortical evoked responses over a two-week period. Compare these responses with those which were recorded 13 days earlier and shown in figure 15. The recording conditions were the same as for figure 15.

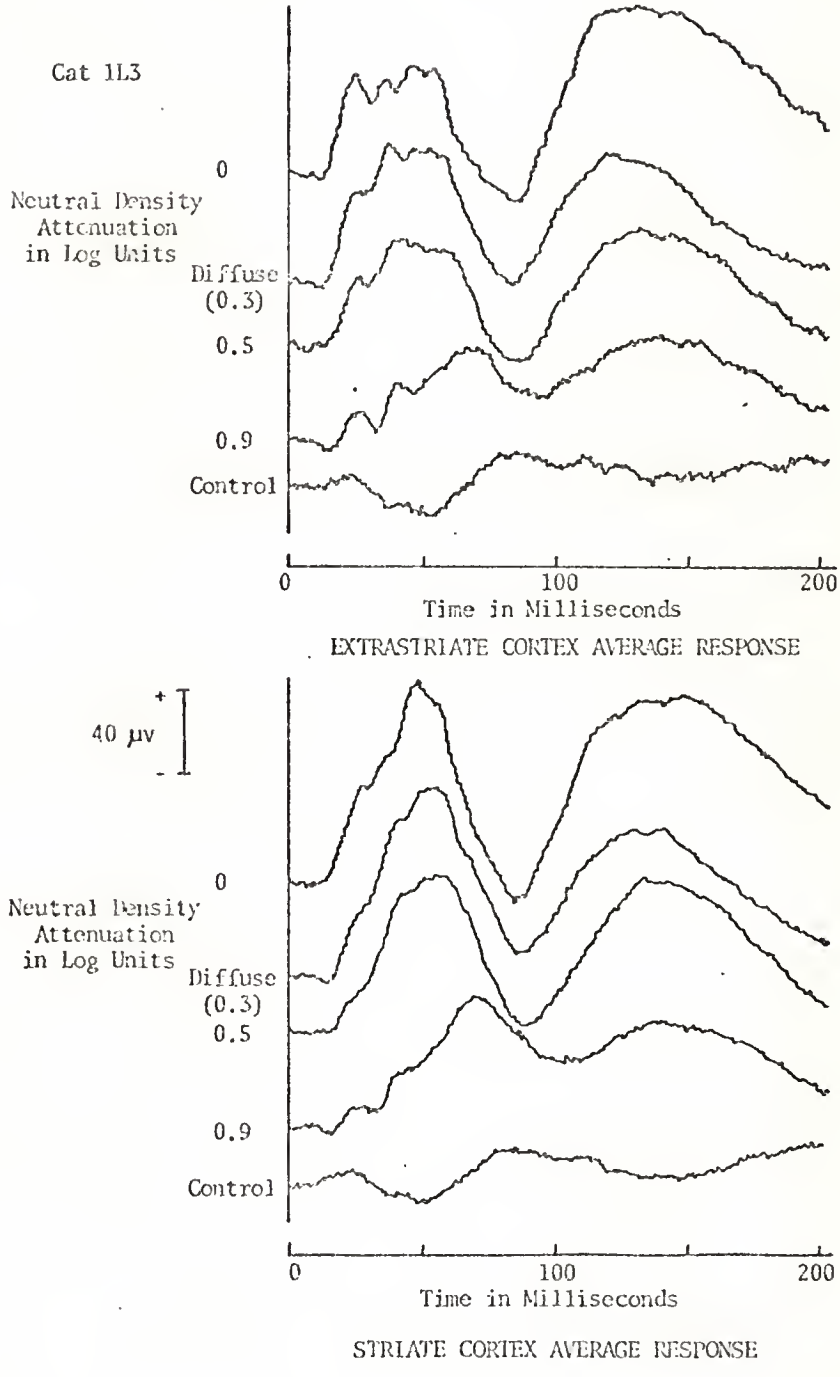


Figure 17. Diffuse flash cortical evoked responses to a series of stimulus intensities. Striate and extrastriate responses were recorded simultaneously. Electrode locations: striate - P3.0, L3.0; extrastriate - P3.0, L8.0 (both epidural).

Figure 18. The effect of pattern feature size upon the cortical evoked responses of cat 1K9. Both the striate and extrastriate responses are sensitive to spatial pattern. 64 sweeps/average. 2.25 seconds between stimulus flashes. Electrode locations: striate - P3.0, L3.0; extrastriate - P3.0, L8.0 (both epidural).
* Difference waveforms are left extrastriate responses minus the upper diffuse response.

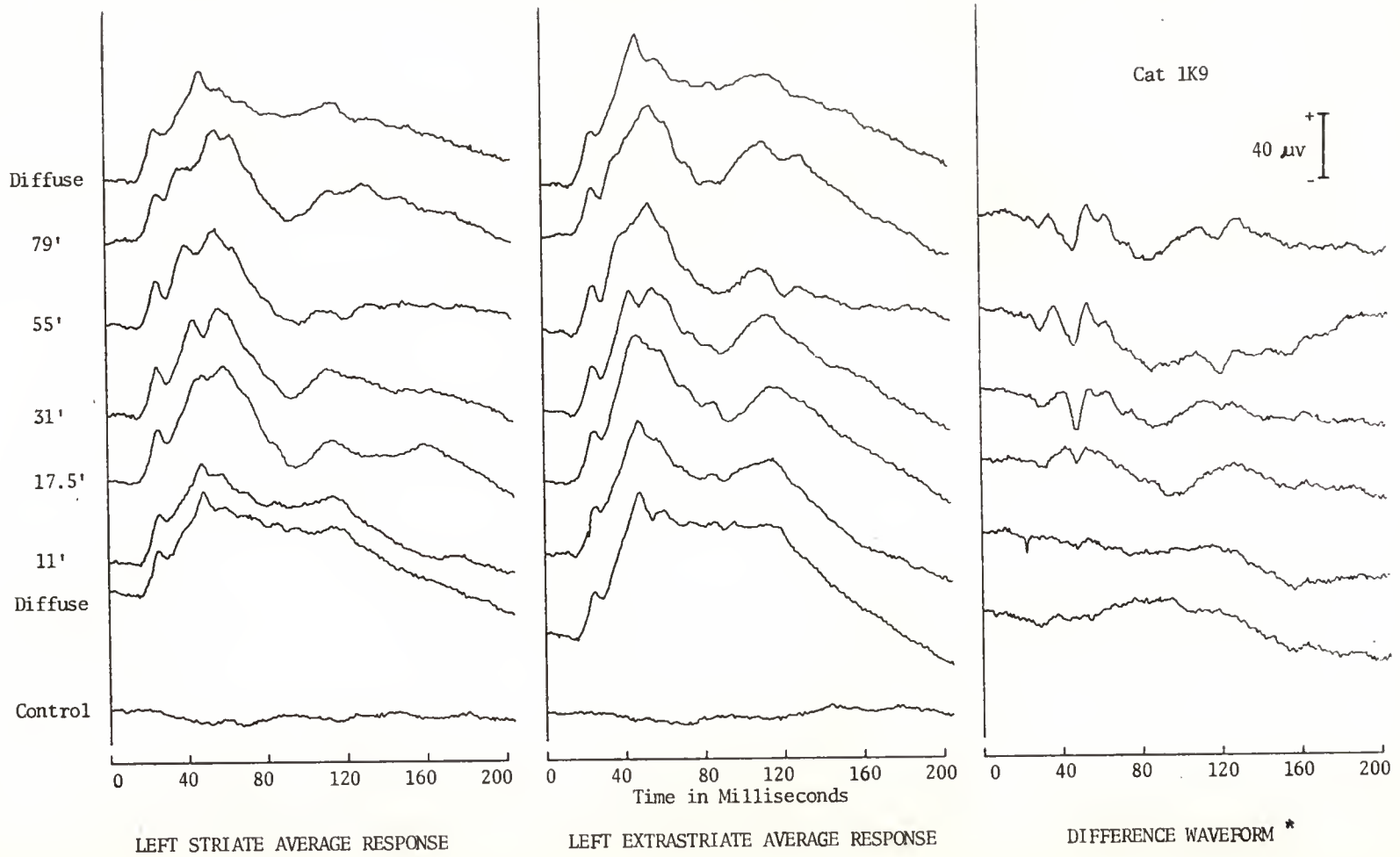

Cat 1K9
40 μv
+
-
Diffuse
79'
55'
31'
17.5'
11'
Diffuse
Control
0
40
80
120
160
200
Time in Milliseconds
LEFT STRIATE AVERAGE RESPONSE
LEFT EXTRASTRIATE AVERAGE RESPONSE
DIFFERENCE WAVEFORM *

Figure 19. The effect of defocus upon responses to a 31 minute of arc per square checkerboard patterned stimulus. Difference waveforms (+0.12 D response - other response) are helpful in determining which features in the response waveform are influenced by quality of focus and to what extent. Cat 1K9 striate electrode. 64 sweeps/average response.

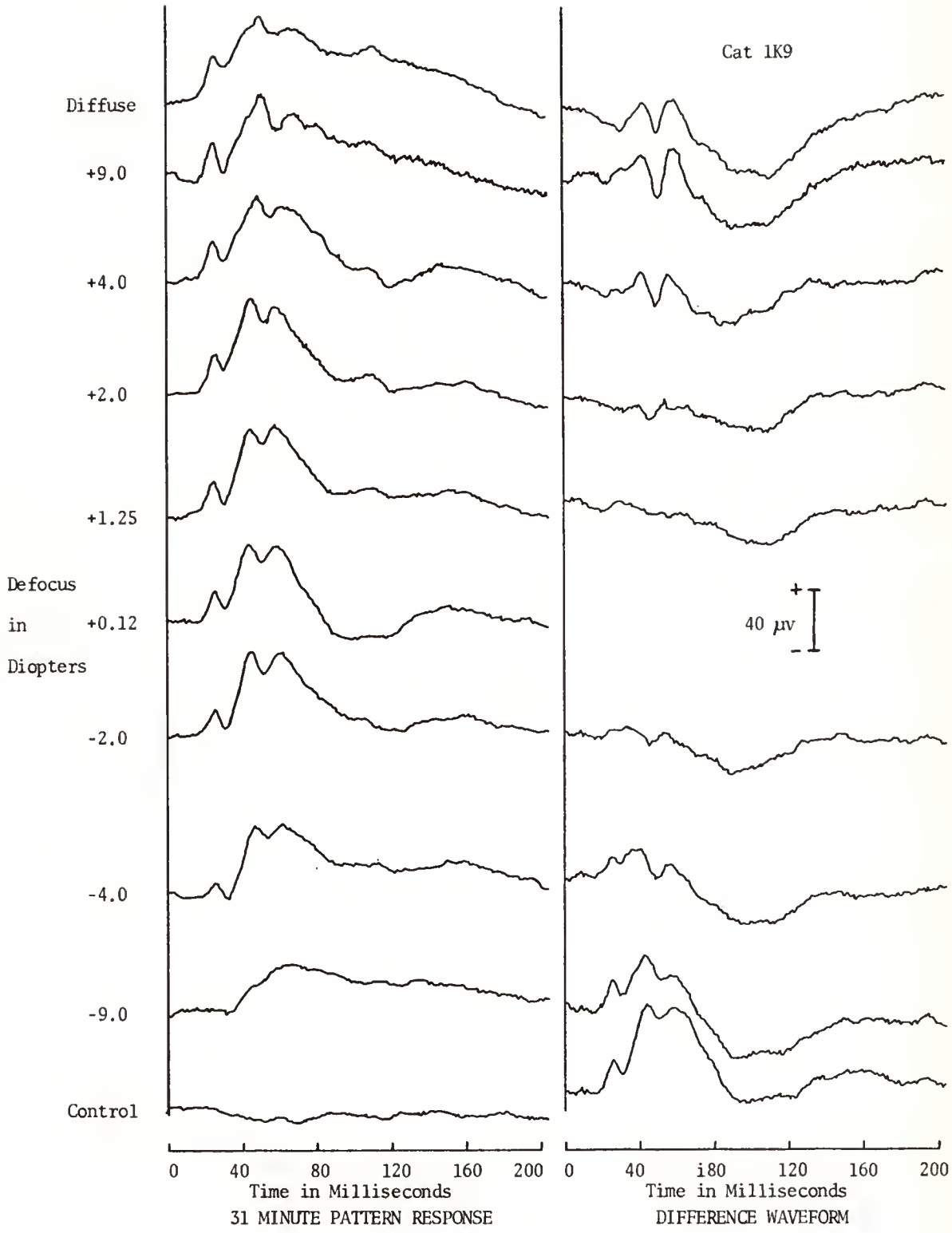

Cat 1K9
Diffuse
+9.0
+4.0
+2.0
+1.25
Defocus
in
Diopters
+0.12
-2.0
-4.0
-9.0
Control
+
40 μv
-
0
40
80
120
160
200
Time in Milliseconds
31 MINUTE PATTERN RESPONSE
0
40
i80
120
160
200
Time in Milliseconds
DIFFERENCE WAVEFORM

Figure 20. The effect of a positive 9 diopter defocus upon responses to patterned stimuli with different feature sizes. Note that there is very little sensitivity of response to pattern when the pattern is defocused by 9 diopters. 64 sweeps/average response.

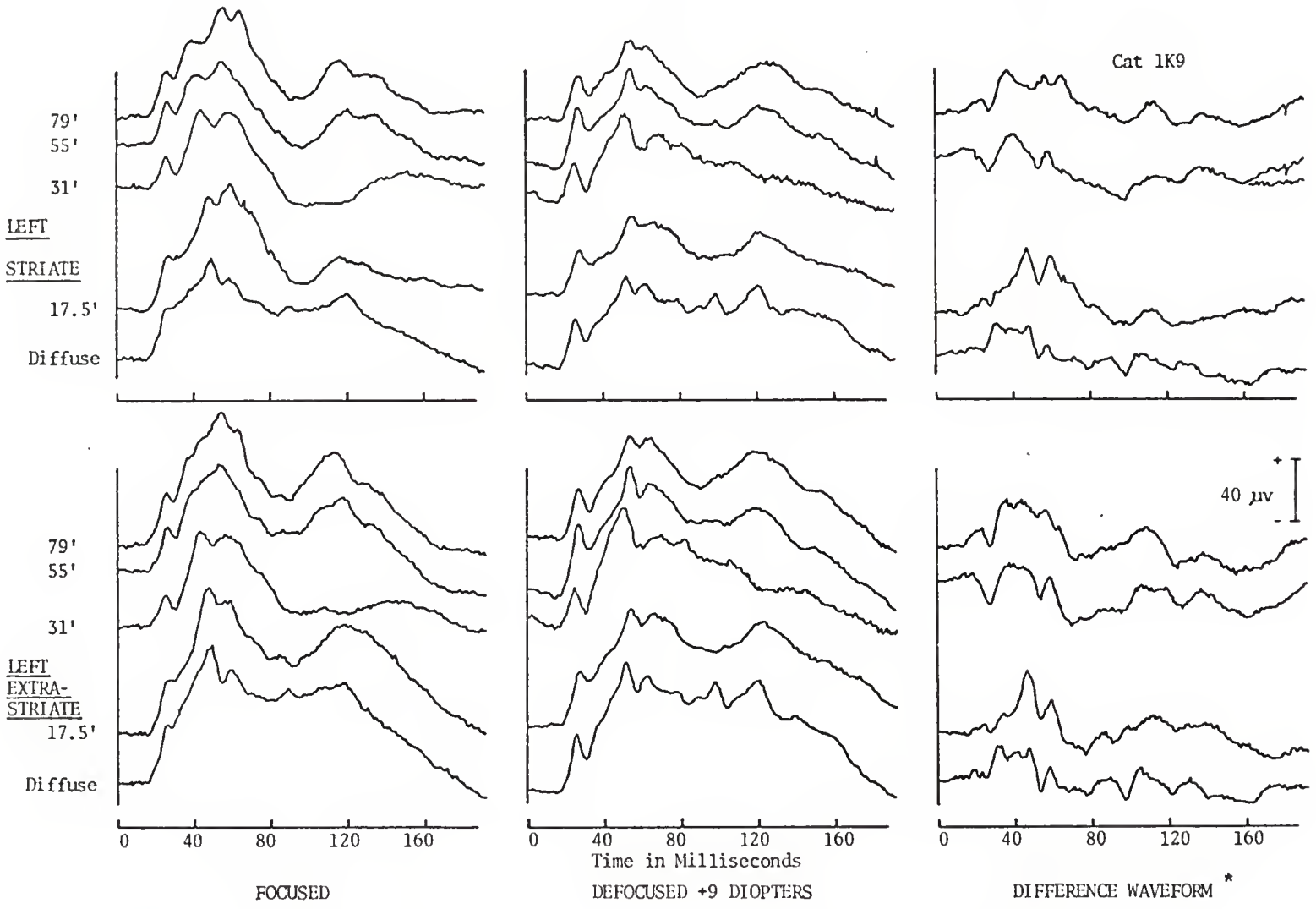
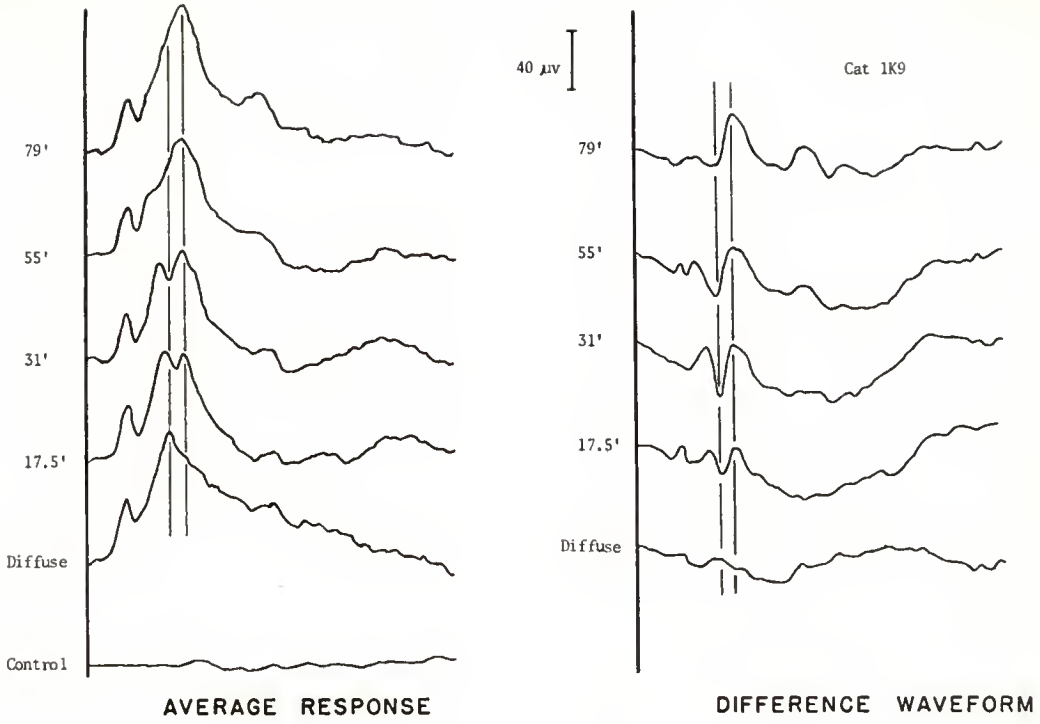
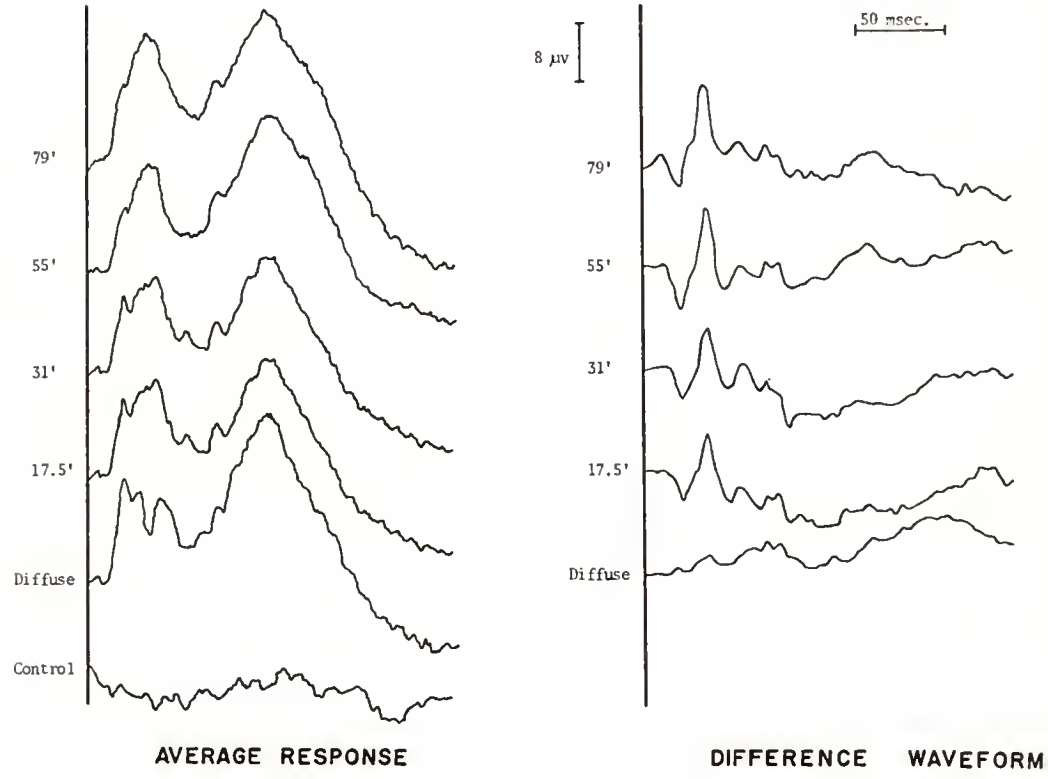

Cat 1K9
79'
55'
31'
LEFT
STRIATE
17.5'
Diffuse
79'
55'
31'
LEFT
EXTRA-
STRIATE
17.5'
Diffuse
+
40 μv
-
0
40
80
120
160
Time in Milliseconds
FOCUSED
DEFOCUSED +9 DIOPTERS
DIFFERENCE WAVEFORM *

Figure 21. Simultaneously recorded optic nerve and cortex responses to diffuse and patterned stimuli. In the cortical responses note that the peak of wave III is at a different latency in the 79 minute pattern response than in the diffuse response.

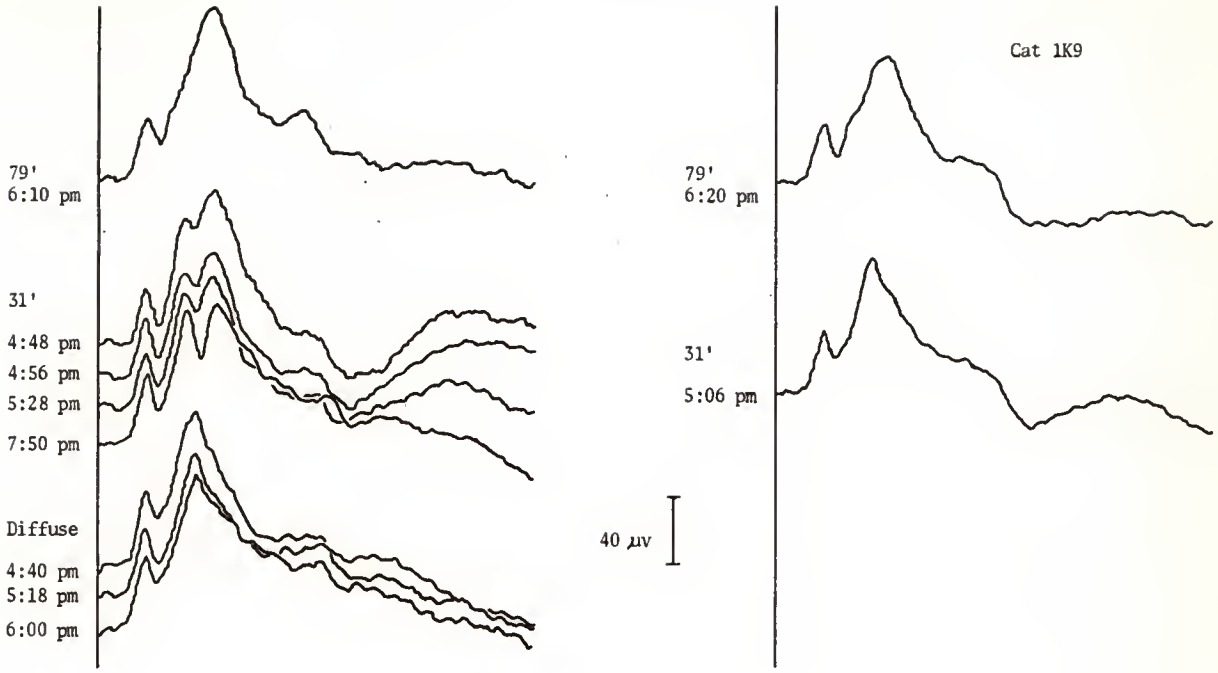


STRIATE CORTEX

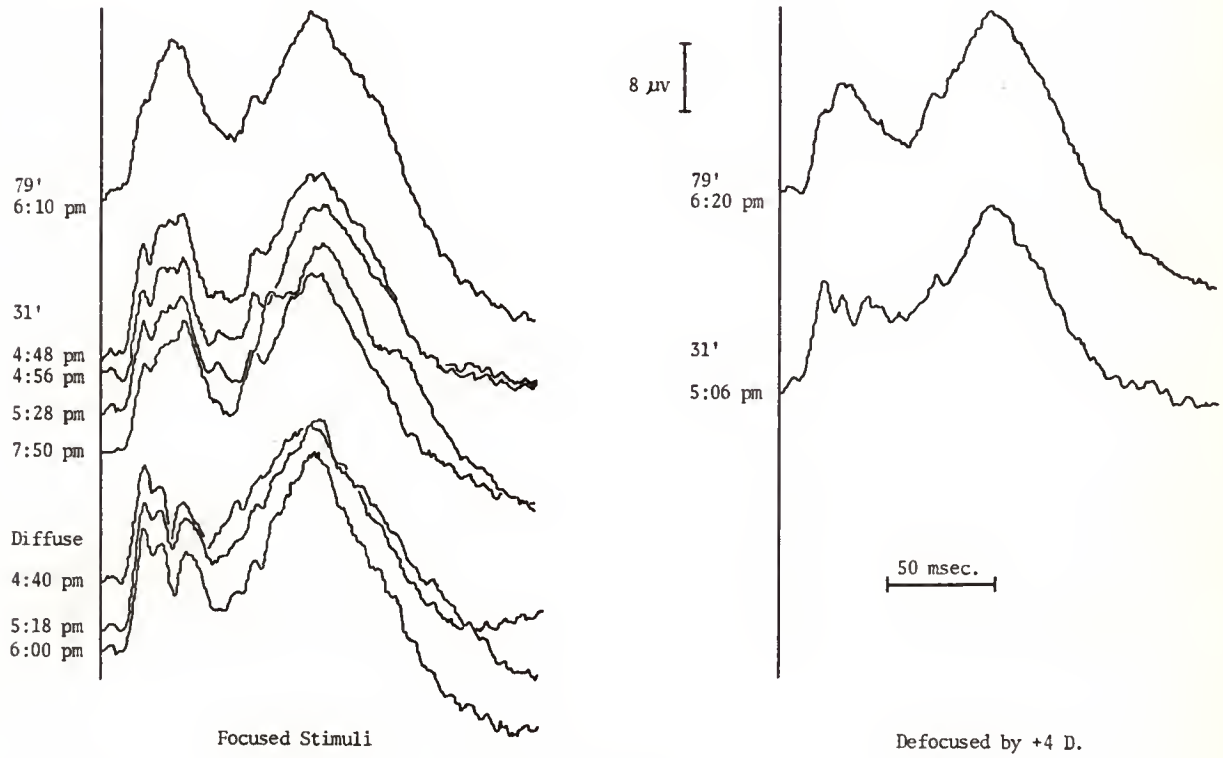


OPTIC NERVE

Figure 22. Repeatability of optic nerve and cortical evoked responses from cat 1K9 within one session. In addition, an example of the effect of 4 diopters of defocus is given.



STRIATE CORTEX



OPTIC NERVE

the shape of waves III, IV, and V was influenced by feature size in both cases. Figure 19 shows the effect of various degrees of defocus upon the response to the 31 minute of arc pattern where defocus was achieved by use of an external lens in the spectacle plane. Figure 20 describes the effect of a constant +9 diopter defocus upon patterns of different feature size. It demonstrates that when well defocused, the feature size of a patterned stimulus did not influence the waveform of the response and that the difference waveform between responses to a focused and a defocused patterned stimulus was very similar to that between responses to a focused patterned stimulus and a diffuse stimulus as shown in figure 18 for data recorded one hour earlier. The external lens was used because the large (1 to 2 degrees of arc per square) patterns to which the evoked responses from the cats in these experiments were found to be sensitive were not well defocused by the maximum use of the range of focus built into the stimulator. Use of different external lenses introduces small changes in pattern feature size on the retina and size of retinal region stimulated, in the form of spectacle magnifications, which will be discussed later.

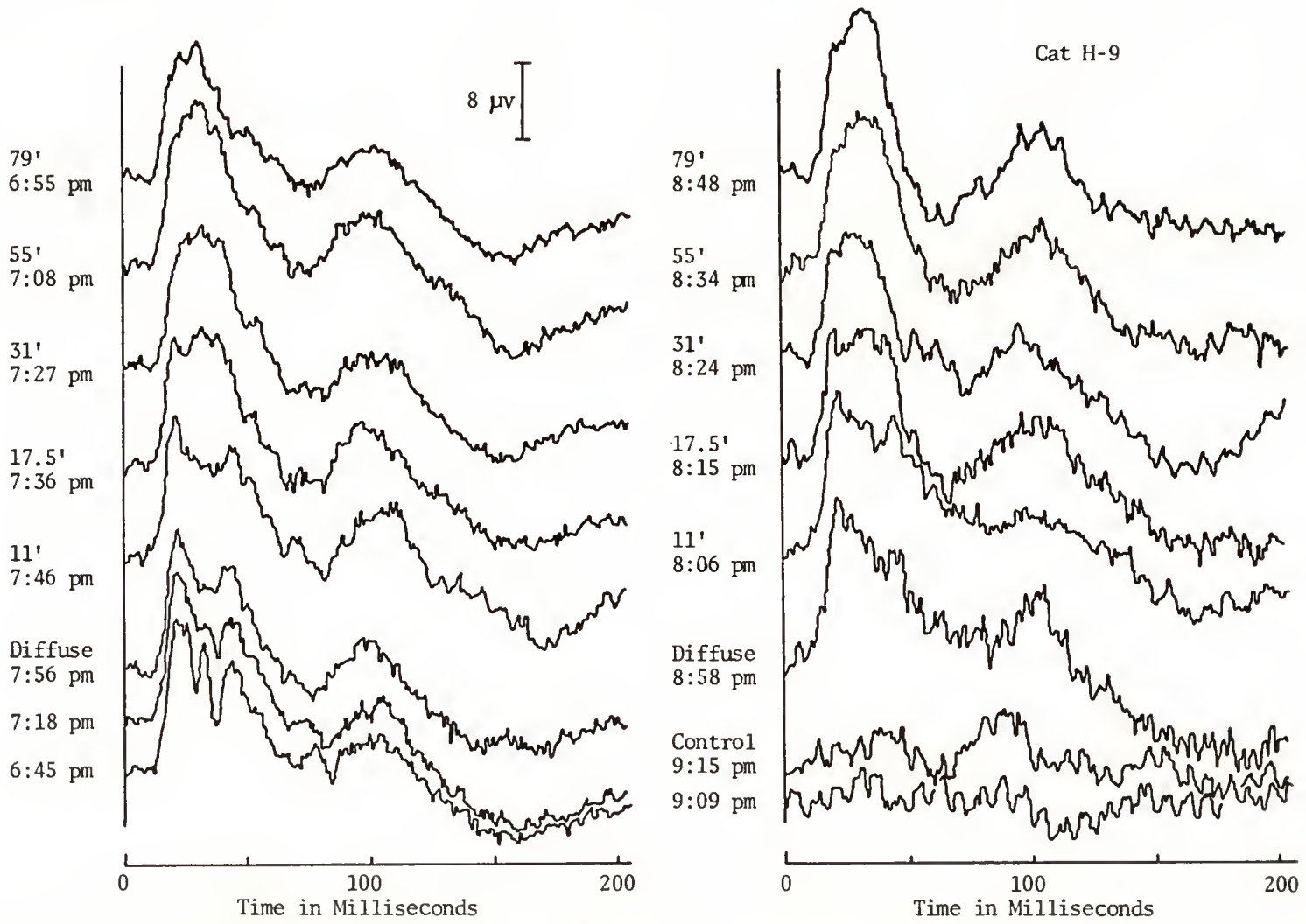
In a second recording session, one week later, both optic nerve and cortex responses were recorded from this same animal. The effect of pattern feature size upon these responses can be seen in figure 21. The agreement of these cortex responses with those recorded one week earlier is evidence for repeatability of this effect within one animal. Also, it is very important to note that the optic nerve responses are sensitive to pattern stimulation and to pattern feature size. Most noticeable is an increase in the positivity of the waveform at a latency of 25 to 35 milliseconds, which is on the late side

of the primary positive peak of an optic nerve response to diffuse stimulation. The repeatability of the responses within one session with this animal was also tested and the results are shown in figure 22. Included in the same figure is an example of the effect of +4 diopter defocus with zero spectacle magnification upon the response to a 31 minute of arc per square pattern and a 79 minute of arc per square pattern. This data indicates that an equal amount of blurring of contrast borders for patterns with different size features does not cause the evoked responses to revert equally well to the waveform characteristic of diffuse stimulation.

A third animal, cat H9, provided excellent data on the optic nerve. For this animal, the effect of pattern feature size is shown in figure 23. There is good agreement between data shown in this figure and that in figure 21. Also, responses to the 11 minute of arc per square pattern are included in this figure and it can be seen that the difference between responses to this pattern and to diffuse is either insignificant or very small. This was a consistent finding from several animals. The control run was taken late in the session and shows that the animal had developed some synchronous EEG activity which was not evident earlier in the session.

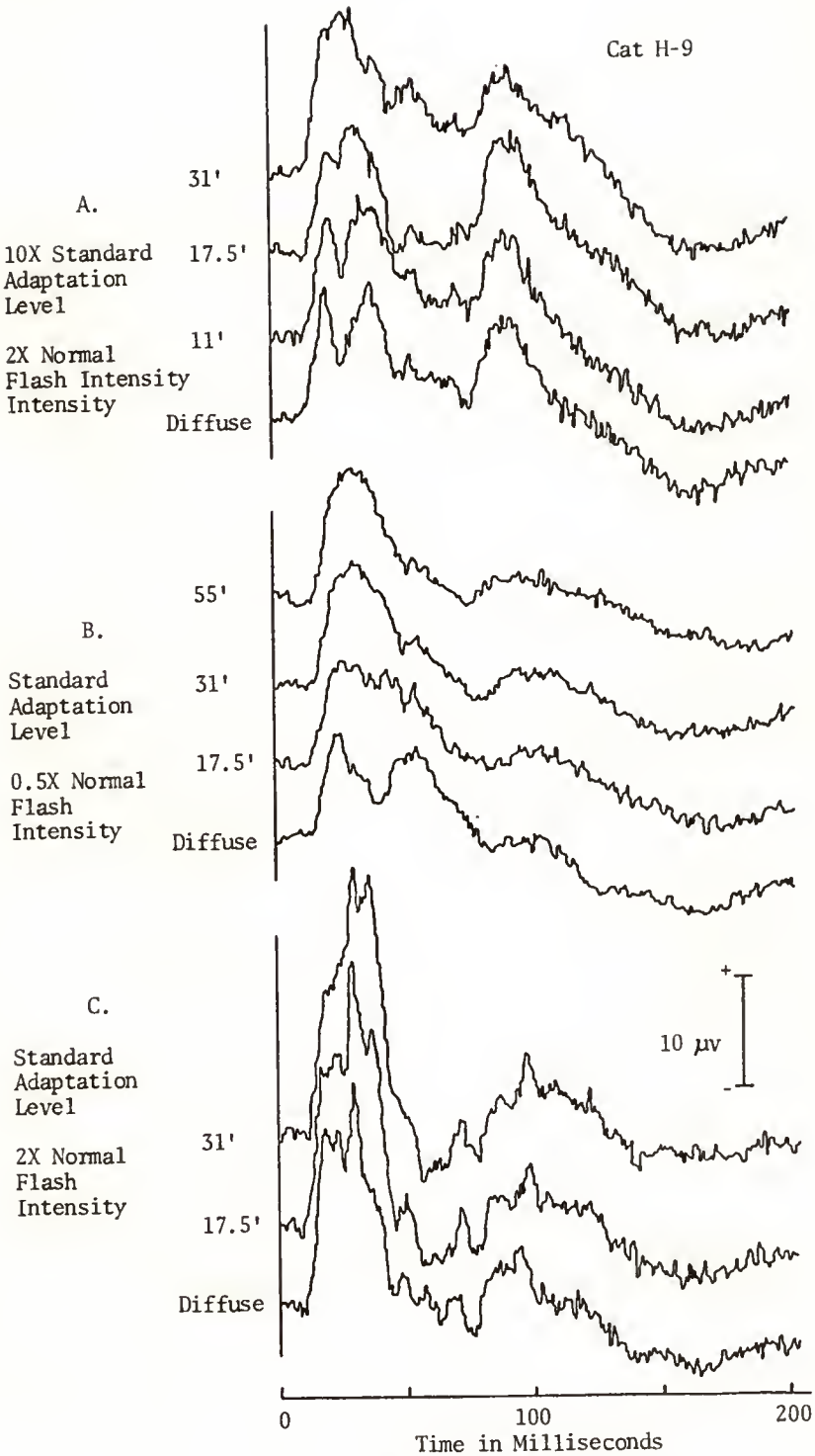
To be assured that the effects of pattern feature size upon the visually evoked optic nerve potential were not absolutely peculiar to one set of adaptation level and stimulus intensity conditions, the recordings given in figure 24 were made with half the normal flash intensity, twice the normal flash intensity, and twice the normal flash intensity at ten times standard adaptation level. Pattern sensitivity of the response was evident under each of these conditions.

Figure 23. The effect of pattern feature size upon the optic nerve responses of cat H-9. Time of run and feature size are given for each response. 128 sweeps/average response.



CAT OPTIC NERVE - AVERAGE RESPONSES

Figure 24. Pattern sensitivity of optic nerve responses at several combinations of adaptation level and flash intensity.



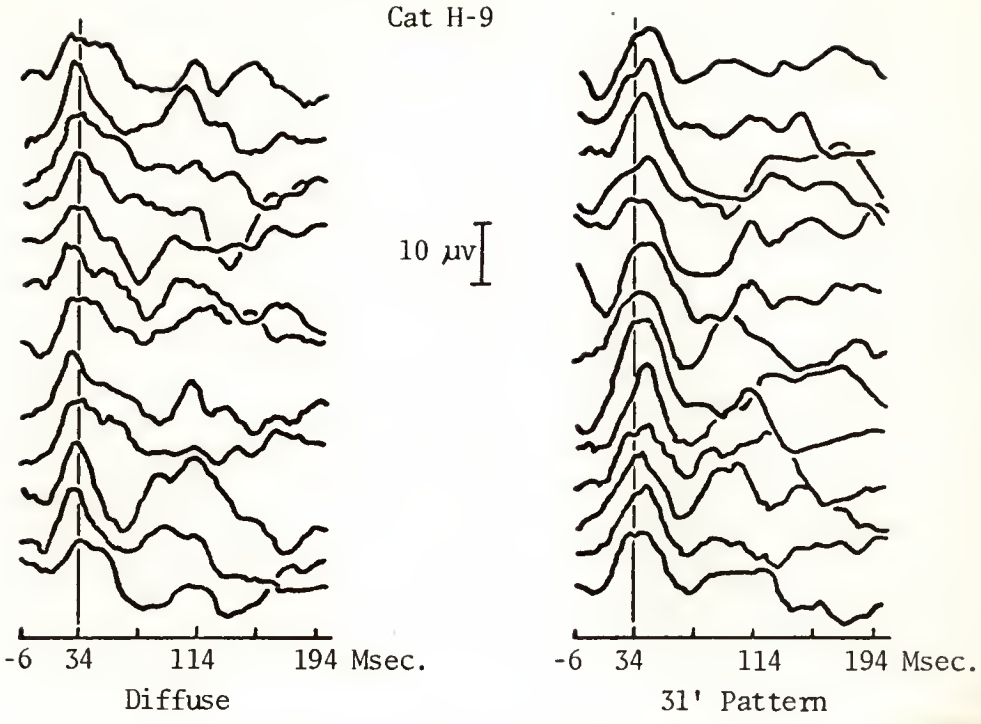
CAT OPTIC NERVE - AVERAGE RESPONSES

A difference in the average response waveforms to two different stimuli implies a difference (on the average) in the individual responses to these stimuli. In figure 25, sets of typical individual optic nerve responses are given. The differences between these sets of individual responses can be seen. For diffuse responses, the largest peak of the primary positivity is at a latency of 30 to 34 milliseconds and a smaller peak or an inflection is usually seen at 55 milliseconds. For the 31 minutes of arc pattern the largest peak of the primary positivity occurs between 40 and 50 milliseconds. In general the agreement between individual and average responses in this set of data is quite good.

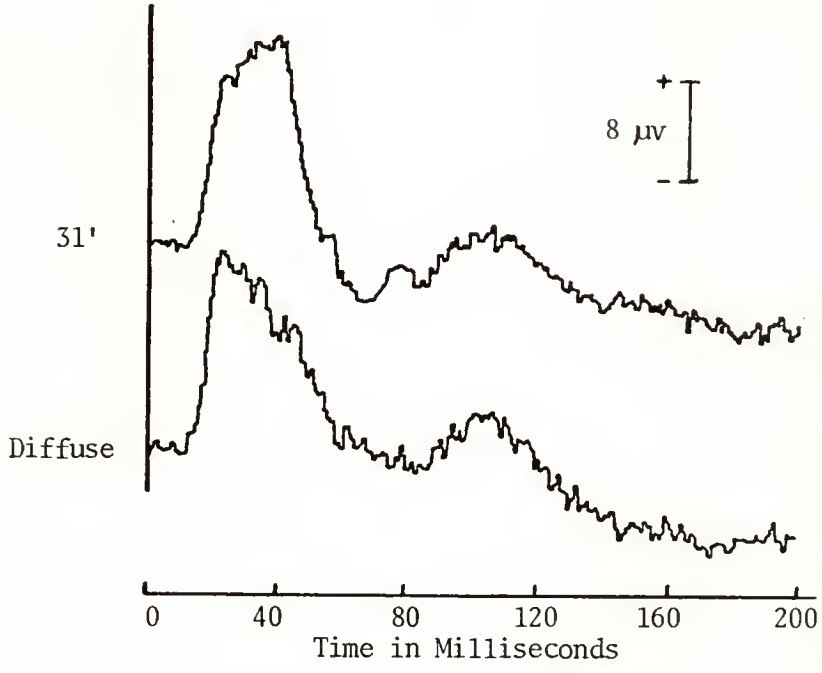
There were no useable cortex electrodes on this animal.

Of the remaining three cats, two provided data on the cortex and two on the optic nerve. These three animals were very large, old, male cats and their responsiveness to pattern was not as clear and vivid as that in the data already given. They were, however, sensitive to pattern. For cat 1L1, typical cortical responses to diffuse and patterned stimuli are given in figure 26 along with difference waveforms. These responses are unusual in that wave IV is small and in the 31 minute of arc response the second peak of wave III is quite large.

Cortex responses of animal 1L16 are shown in figure 27. They are repeatable within one session. A negative-positive-negative sequence is seen in these responses in the time period normally occupied by a single negative-going wave IV. Optic nerve responses from this same animal are shown in figure 28 along with their difference waveforms.



INDIVIDUAL OPTIC NERVE RESPONSES



AVERAGE OPTIC NERVE RESPONSES

Figure 25. Simultaneously recorded individual and average optic nerve responses to diffuse and patterned stimuli. Cat H-9.

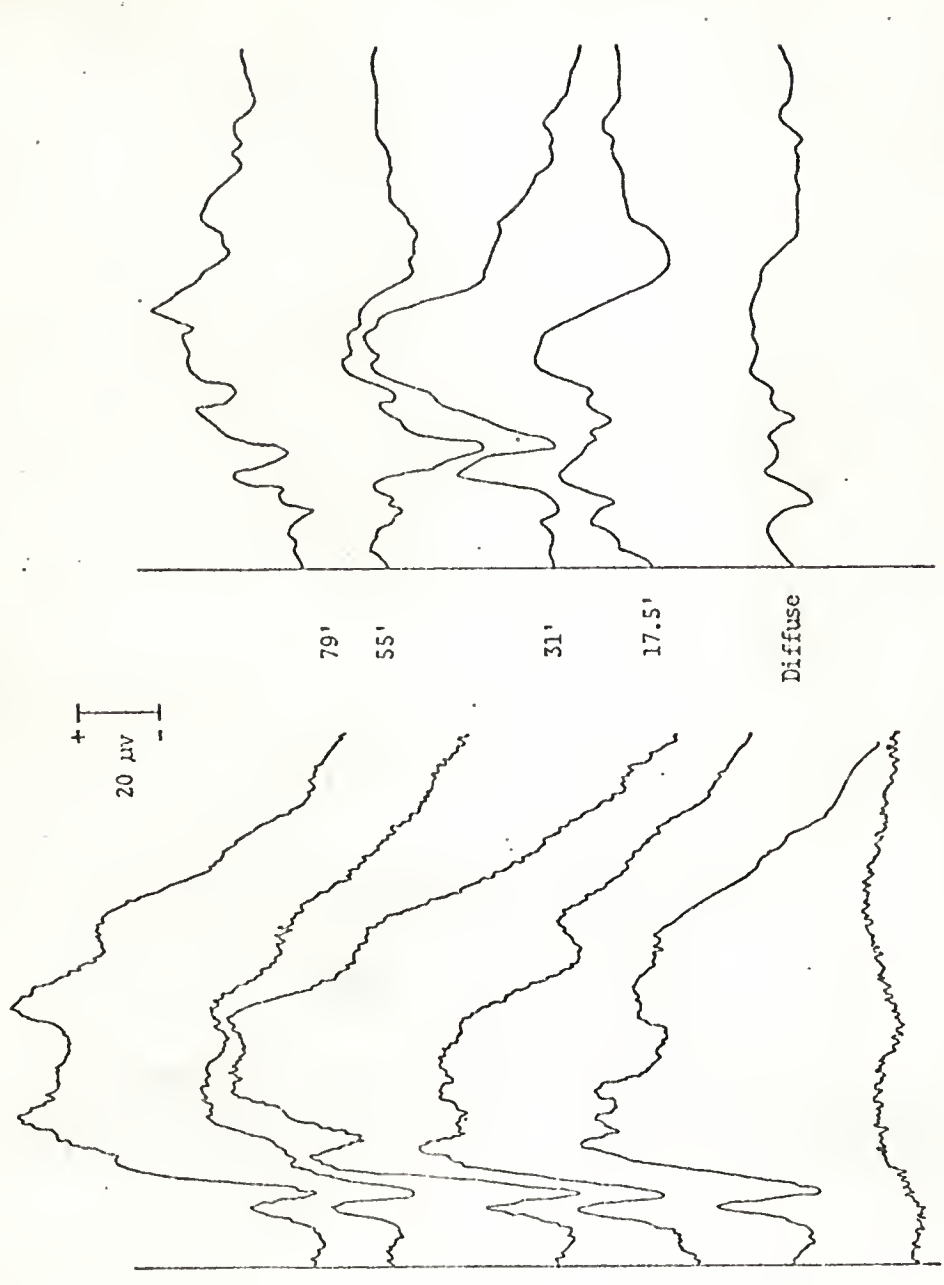


Figure 26. The effect of pattern feature size upon cortical evoked responses of cat 1L1.

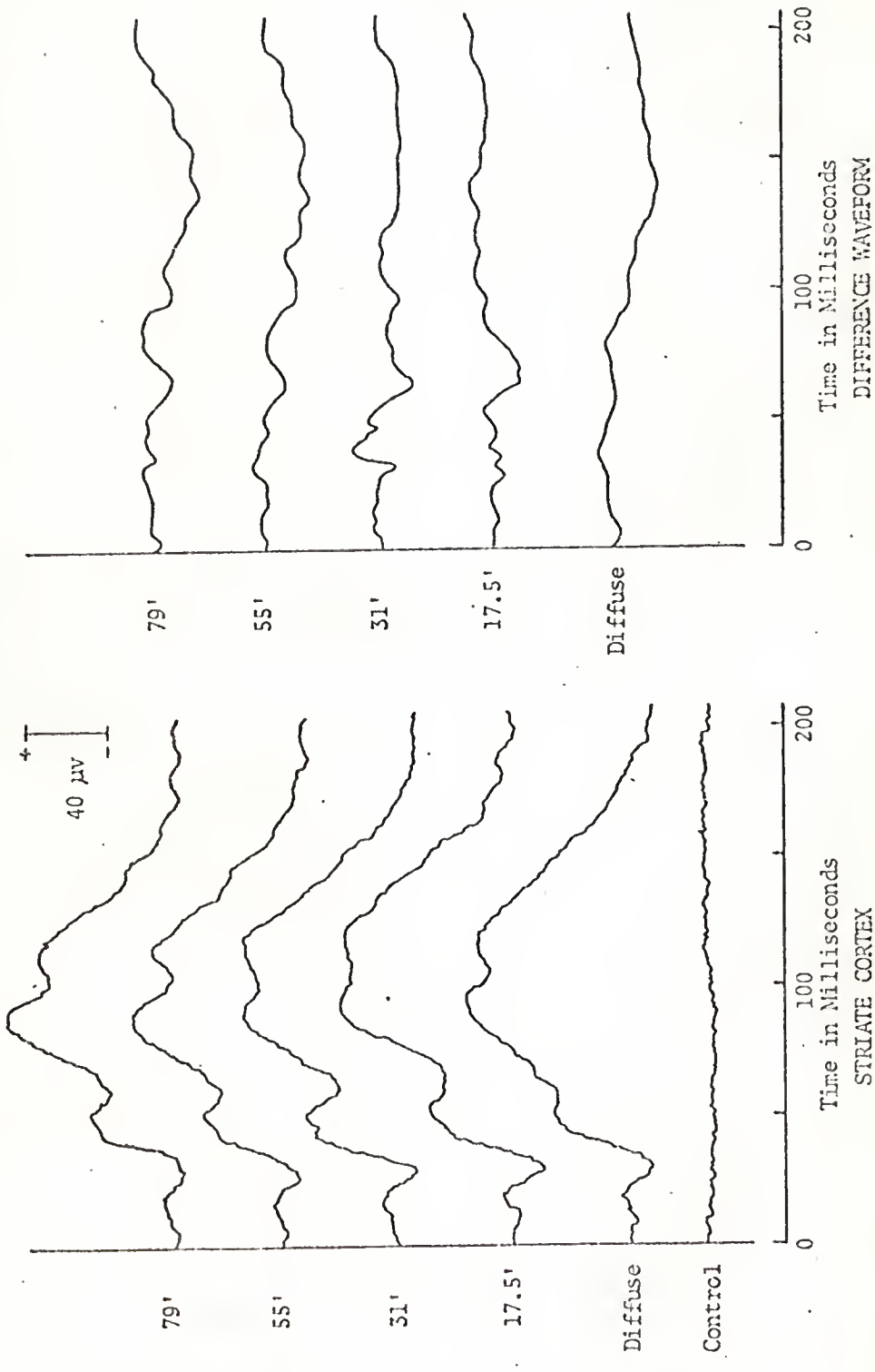


Figure 27. The effect of pattern feature size upon cortical evoked responses of cat 1L16.

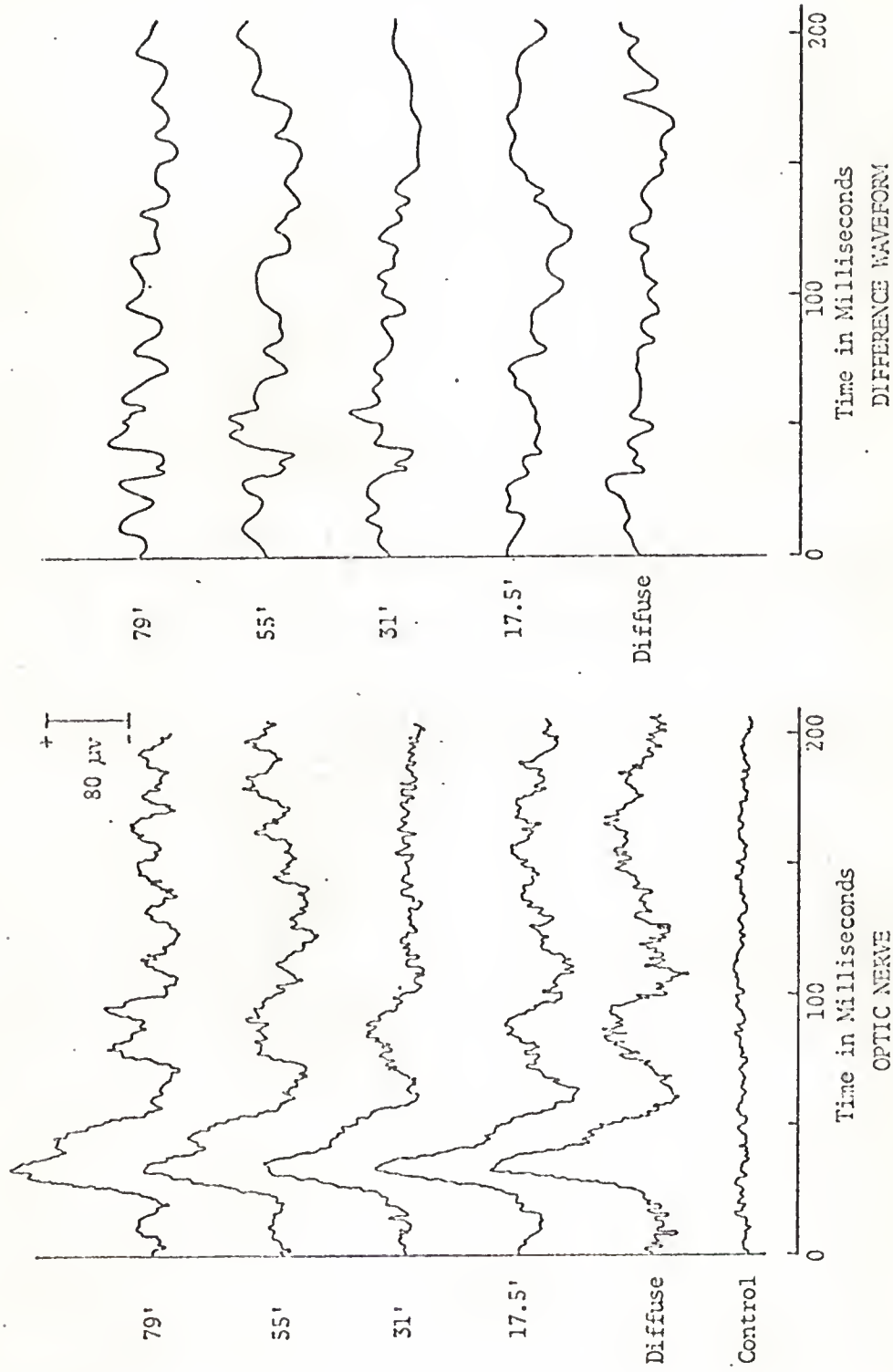


Figure 28. The effect of pattern feature size upon optic nerve responses of cat 1L16.

From the sixth cat, 1L6, optic nerve responses are given in figure 29. All responses from this animal were taken with standard adaptation level and twice normal flash intensity.

In general, for all four cats from which optic nerve data were obtained, the effect of patterned stimulation as opposed to diffuse stimulation on the optic nerve response was consistent. Observation of the responses and the difference waveforms shows that either the slope of the rise to the primary positive peak, or the amplitude of the early side of the peak, is slightly reduced, and either the amplitude of the late side of this peak increases, or a second positive peak or inflection develops on the downward slope. The effect of pattern feature size appears to modulate the extent to which the changes in waveform just described occur.

There is considerable variation between cats in the cortical evoked response to diffuse flash. For this reason, the effect of patterned stimulation must be judged with respect to the diffuse flash response of the same animal. In the response to a pattern of medium sized features (approximately 30 minutes of arc per square), waves I and II are usually unchanged, a double peak on wave III is either developed or enhanced, and when they can be identified, waves IV and V usually increase in size.

The smallest effective pattern feature size used was 17.5 minutes of arc per square. The largest feature size used (79 minutes) was effective. The most noticeable effect of pattern feature sizes within this range was to modify the amplitude and latency of the peaks of wave III.

Responses of the lateral geniculate nucleus were recorded

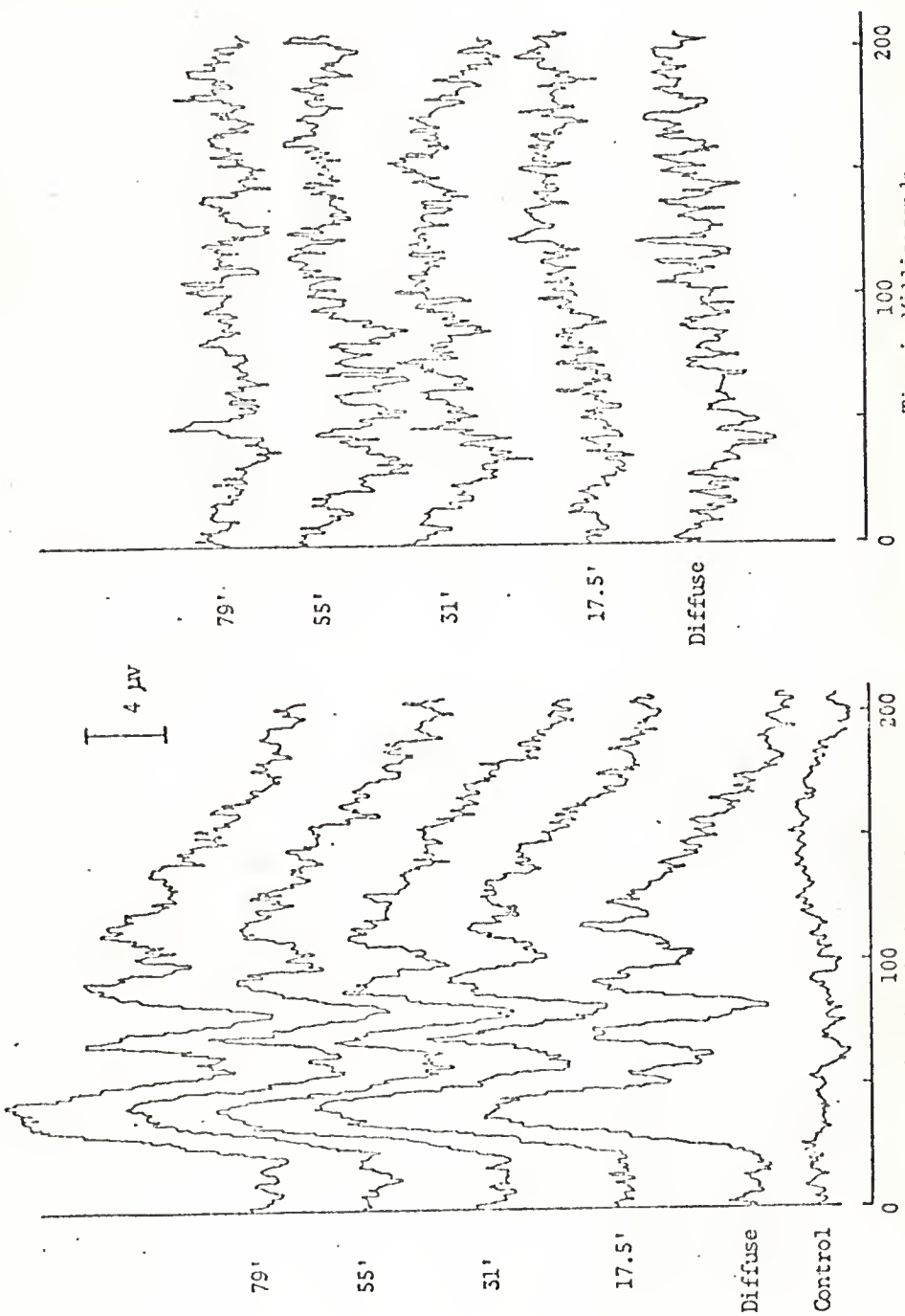


Figure 29. The effect of pattern feature size upon optic nerve responses of cat 1L6.

(using bipolar wire electrodes) from five of these cats simultaneously with those from optic nerve or cortex. No consistent effect of patterned stimulation was identified.

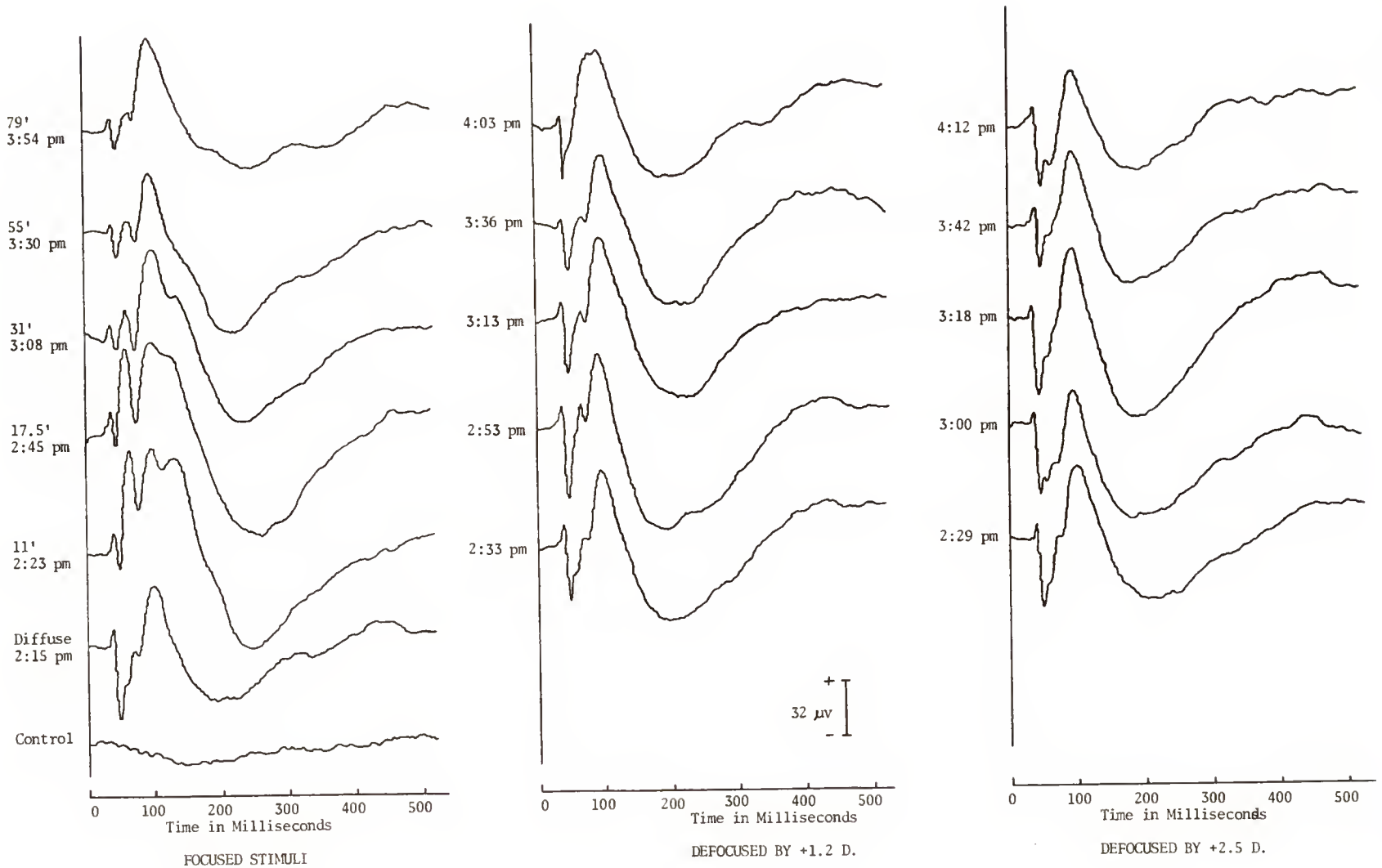
Maxwellian View Stimulation of Monkey

Visually evoked responses from an epidural electrode over striate cortex of a paralyzed rhesus monkey are shown in figures 30 and 31. These responses were obtained during a 7½ hour recording session within which the animal heart rate, body temperature, and expired CO_2 were very stable at normal values. At the end of the session this animal recovered rapidly from the neuromuscular blockade and was in good health. There was a clearly visible sensitivity of this response to pattern feature size. Within this session, pattern feature sizes were repeated and the responses were consistent.

In terms of their polarity and latency (in milliseconds), the peaks which are starred in figure 31 are P39, N46, P67, P96, P124, and N240. The difference between a pattern response and a diffuse response is best described by the difference waveform in figure 31. It is important to recognize that the difference waveform is not small; it is larger in amplitude than the diffuse response. Responses from this animal indicate that the effect of pattern feature size is to control the magnitude of the activity represented by the difference waveform shown, without changing the latency of the difference waveform peaks.

A response to a defocused patterned stimulus is less different from a diffuse response than is a response to a well focused patterned stimulus. To defocus a patterned stimulus to the extent that the

Figure 30. Responses of a paralyzed rhesus monkey to spatially patterned visual stimuli. Each stimulus was projected onto the macular region using the Maxwellian view pattern stimulator. The effects of pattern feature size, and +1.2 and +2.5 diopters of defocus are displayed. These recordings are from a chronically implanted epidural electrode within 1 degree of the foveal representation in striate cortex. The indifferent electrode was a stainless steel wire loop under the scalp over frontal cortex. An average response contains 64 individual responses to flashes 2.25 seconds apart.


79'
3:54 pm
55'
3:30 pm
31'
3:08 pm
17.5'
2:45 pm
11'
2:23 pm
Diffuse
2:15 pm
Control
0 100 200 300 400 500
Time in Milliseconds
FOCUSED STIMULI
4:03 pm
3:36 pm
3:13 pm
2:53 pm
2:33 pm
+
32 μv
-
0 100 200 300 400 500
Time in Milliseconds
DEFOCUSED BY +1.2 D.
4:12 pm
3:42 pm
3:18 pm
3:00 pm
2:29 pm
0 100 200 300 400 500
Time in Milliseconds
DEFOCUSED BY +2.5 D.

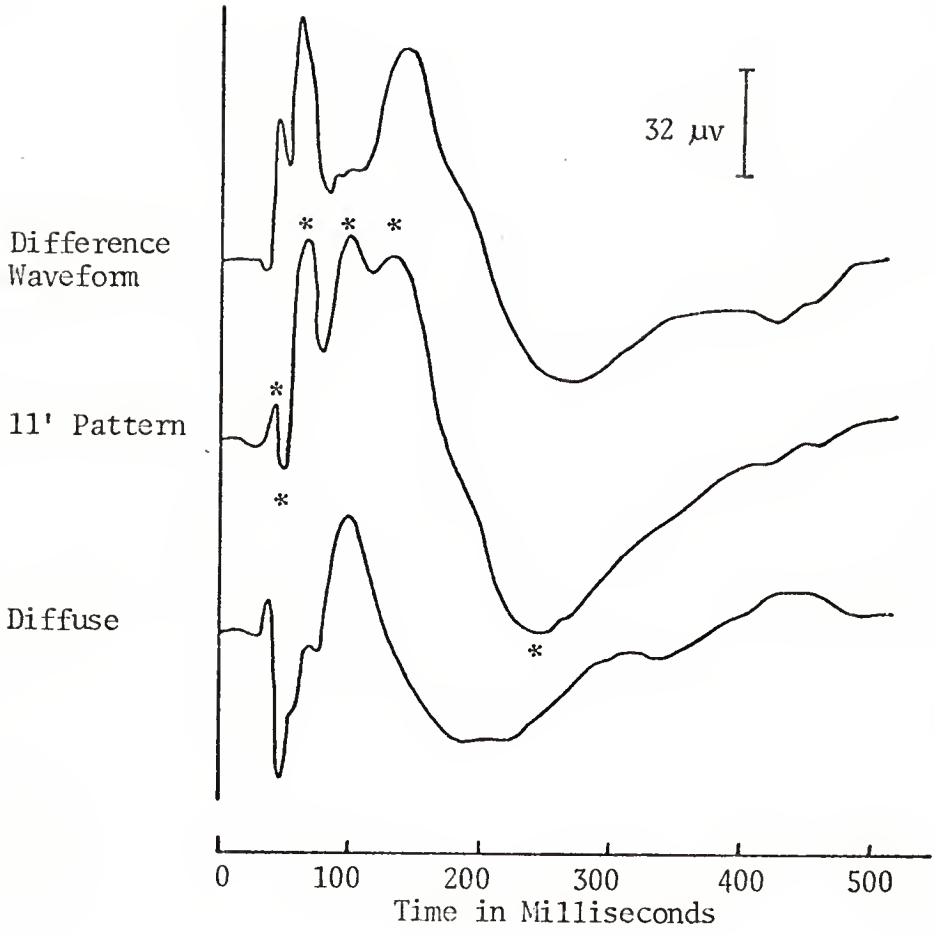


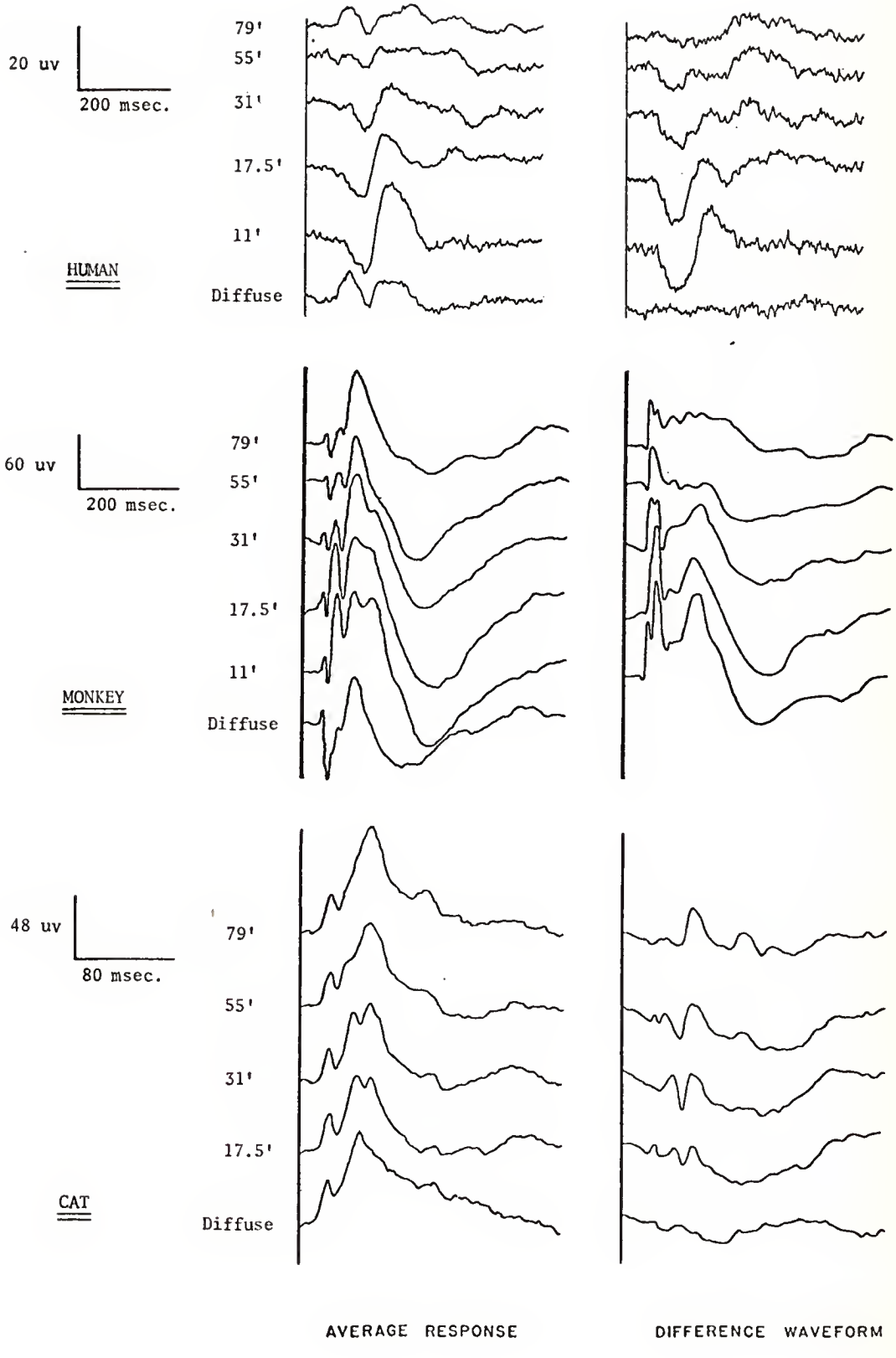
Figure 31. Comparison of the evoked responses of rhesus monkey to an 11 minute pattern and to diffuse stimulation. The difference waveform (pattern - diffuse) indicates that the change in the activity evoked within the visual system between these two cases is large and that rhesus monkey is a good animal in which to study the generation of visual evoked potentials using both patterned and non-patterned visual stimuli. Asterisks mark peaks at latencies of 39, 46, 67, 96, 124, and 240 milliseconds. Recording conditions are the same as in figure 30.

related response is identical to a diffuse response, fewer diopters of defocus are required for a pattern of small feature size than for a pattern of larger feature size, at least within the feature size range used in this experiment. Note that for this animal, the minimum dioptric value of defocus necessary to effectively eliminate sensitivity to a patterned stimulus was less than or equal to 1.2 diopters for an 11 minute pattern and approximately 2.5 diopters for a 55 minute pattern.

Summary of Results

The results which have been presented show that the visually evoked responses of human, cat, and rhesus monkey cortex and cat optic nerve are sensitive to spatial pattern. Since the sensitivity of human visually evoked responses to checkerboard patterned stimuli had already been established, responses were recorded from human subjects primarily to demonstrate that the procedures and instruments used were effective. Difference waveforms which are helpful in appreciating and comparing the sensitivity of the response to each of the stimulus conditions were derived from the recorded responses. For cat and monkey, evidence for sensitivity to pattern was obtained by comparison of responses to diffuse stimulation and patterned stimulation which provided the same average retinal illumination. Responses to the diffuse stimulus and to patterns of different feature size were different and repeatable (see figure 32). The effect of quality of focus upon responses to patterned stimuli was studied within this project primarily as a control measure to obtain evidence that pattern features and not

Figure 32. Summary of the effects of pattern feature size upon the visually evoked responses from the cortex of human, rhesus monkey, and cat. The responses of each species are pattern sensitive. 64 sweeps/average response.


20 uv
200 msec.
79'
55'
31'
17.5'
11'
Diffuse
HUMAN
60 uv
200 msec.
79'
55'
31'
17.5'
11'
Diffuse
MONKEY
48 uv
80 msec.
79'
55'
31'
17.5'
Diffuse
CAT
AVERAGE RESPONSE
DIFFERENCE WAVEFORM

some minute intensity differences or other factors were the cause of the waveform changes observed in the evoked responses. For cat, it was also shown that cortical responses were sensitive to pattern under several conditions of adaptation level and flash intensity, and that responses characteristic of a patterned stimulus were not obtained using diffuse stimulation with flash intensities greater or less than the intensity normally used. Sensitivity of optic nerve responses of cat to patterned stimuli was observed in individual as well as average responses.

DISCUSSION

Human Subjects

The evoked responses of human subjects to diffuse and patterned visual stimuli were recorded by two methods, the visual fixation task and the Maxwellian view stimulation. By comparison of these two sets of data it is evident that the two methods were not equally effective. Only one of the four subjects was recorded from by both methods. The results were consistent; the responses obtained using the Maxwellian view stimulator were more vividly responsive to pattern than those obtained using the behavioral task. It is now evident that although the responses obtained during use of the behavioral task were pattern sensitive, additional development of this technique is needed to improve its effectiveness. The ultimate goal should be to make these two methods equally effective so that working with monkeys, the same animals could be tested first with the behavioral task and second when stimulated by the Maxwellian view method.

Cat

Data presented in the results of this dissertation indicate that the visually evoked responses of cat optic nerve and visual cortex are sensitive to spatially patterned stimuli. It is reasonable to expect the pattern sensitivity of these responses to be related to the quality of the optics of the eye, retinal grain or ganglion cell density, and ganglion cell dendritic field sizes.

The most recent and very well done work on the quality of optics of the cat eye is that of Wässle (1971). In figure 33 the modulation transfer function (MTF) determined by Wässle is compared with the feature sizes of checkerboard patterns available for use with the Maxwellian view stimulator. The MTF is based upon sinusoidal frequency components. An intensity profile obtained by a scan across a checkerboard pattern would be a squarewave. From the analysis of a squarewave, it is known that given a system with a squarewave applied to its input, the system's transfer function must pass the fundamental, third, and fifth harmonics reasonably well in order for the output to approximate a squarewave. In this figure horizontal line segments that are terminated at the left end with vertical dashes which indicate the fundamental spatial frequency, and which are terminated at the right end with a triangle which indicates the fifth harmonic frequency, are used to indicate the spatial frequency range necessary to transmit a checkerboard pattern with the feature size indicated onto the retina and maintain reasonably sharp contrast borders on the features.

Data from this research shows the evoked responses of cat to be sensitive to patterns with feature sizes from 79 minutes of arc per square (the largest pattern used) down to 17.5 minutes of arc per square. It was a consistent observation that stimulation with the pattern having a feature size 11 minutes of arc per square produced responses which were not noticeably different from diffuse flash responses. The pattern of feature size 5 minutes of arc per square was rarely used with cats. These features are smaller than the visual acuity of cats as determined by behavioral testing (Dews and Wiesel,

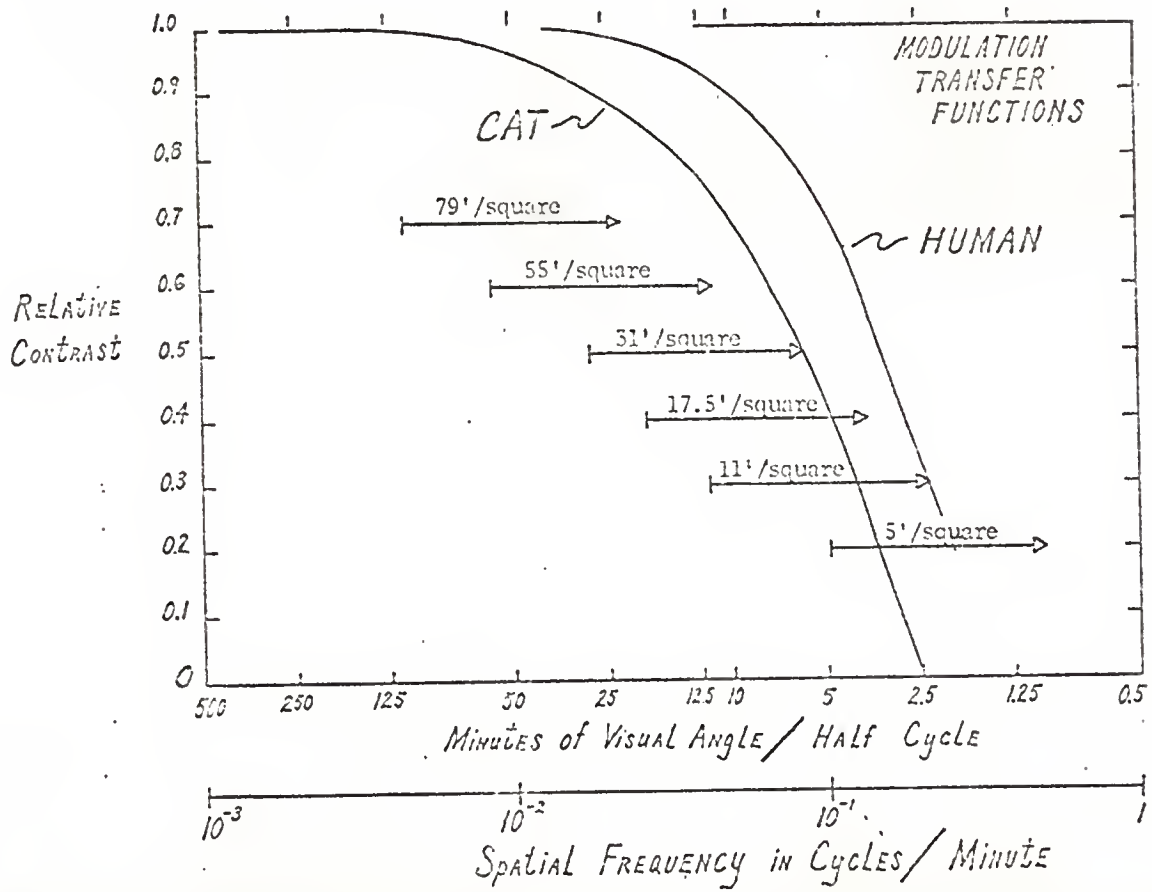


Figure 33. Comparison of the spatial frequency range of the major components of checkerboard patterns with modulation transfer functions for the optics of the cat eye and the human eye (MFT's from Wassle, 1971). The frequency range indicated for each pattern feature size extends from the fundamental indicated by the vertical dash to the 5th harmonic undicated by the triangle.

1970; Smith, 1936). Thus the finest pattern for which a sensitivity of the evoked response was noticeable, that is 17.5 minutes of arc per square, in terms of the fundamental, third, and fifth harmonics of the spatial frequency of the pattern should be represented in the retinal image at relative contrasts of 0.85, 0.57, and 0.27 respectively. For the 11 minute pattern, these values are 0.75, 0.35, and 0.0; which indicates that for the retinal image of the 11 minute pattern, the amount of blur due to non-ideal optics of the eye is quite significant.

The largest pattern feature size used in these experiments did produce responses which were sensitive to patterned stimulation, therefore no statement can be made from this data concerning the largest pattern feature size that is effective for producing responses which are noticeably different from those to diffuse flash. Since for the larger patterns, the frequency components which are important to the production of a good retinal image reach the retina with relative contrasts close to 1.0, the optics of the eye do not limit the sensitivity of the visual system to pattern feature sizes of 1.5 degrees of arc per square and larger. Ganglion cell density in the cat retina has been mapped by Stone (1965) and the distribution is unimodal with its maximum at the center of area centralis.

The region of retina with finest retinal grain, area centralis, should be the region which responds best to small pattern feature sizes. The effect of retinal location was not deliberately studied in this research. The retinal region stimulated was always centered on area

centralis, but the overall size of the region stimulated was large enough to allow the question, where within the region are the cells which respond most vigorously to each of the effective pattern feature sizes located, to arise.

Dendritic field sizes for the giant ganglion cells in the retina of cat have been determined by Honrubia and Elliot (1970) using silver stained whole retina flat mounts. They found the dendritic fields for cells in the center of area centralis to be approximately 70 microns in diameter. Field size increases as distance from the center of area centralis increases. It is interesting to observe the correspondence between the smallest field size measured by Honrubia and Elliot and the size on the retina of the smallest pattern feature which was effective in modifying the waveform of the evoked response (17.5 minutes of arc = 68 microns on the retina). Leicester and Stone (1967) have measured dendritic field diameters of the smaller (not giant) deep multidendrite ganglion cells of the cat retina and report the range to be 70 to 710 microns, the same as found for the giant ganglion cells. Rodieck and Stone (1965) have reported the electrophysiologically determined receptive field centers of giant ganglion cells of cat to range from 85 to 880 microns.

In the present dissertation research, the retinal region stimulated was rectangular, 9 by 13.5 degrees, and centered on the area centralis. Therefore, the perimeter of the retinal region stimulated was 4 to 7 degrees from the center of area centralis. At this distance, Honrubia and Elliot show giant ganglion cell dendritic field diameters to range between 200 and 300 microns. The largest pattern feature size

used in these experiments was 306 microns per square and therefore squares of this size at the perimeter of the pattern should have stimulated ganglion cells quite effectively. For each of the 4 effective pattern feature sizes used, an annulus of ganglion cells in the retina had dendritic fields which matched in size the features of the pattern.

If the set of ganglion cells responding most strongly to each of these patterns was different, there are several possible approaches for testing this hypothesis. One could stimulate a smaller retinal region and compare the pattern feature size which evokes the best response to pattern when area centralis is stimulated with the feature size which is most effective when the region stimulated is 4 to 7 degrees from the center of area centralis or even more peripheral. Another interesting approach would be to create a patterned stimulus containing a series of feature sizes with the smallest feature size in the center of the pattern and matched in size to the known size of ganglion cell dendritic fields in the area centralis, and progressively larger features in the more peripheral portions of the pattern. Responses to this pattern could be compared to responses to patterns each containing only one feature size.

Data presented in the results of this dissertation indicate that there is a consistent effect of patterned stimulation upon the optic nerve response: the slight reduction in the slope or amplitude of the rise to the primary positive peak of the response and usually quite noticeable increase in the positivity on the late side of this

peak. This finding may relate to the observation of Rodieck and Stone (1965) and Barlow et al. (1964) that stimulation of ganglion cell receptive field centers produces activity with a shorter latency than stimulation of the receptive field surround. Rodieck and Stone note that the activity in response to surround stimulation may be up to 60 milliseconds later than that evoked by center stimulation alone. Since stimulation of the whole receptive field normally produces a response characteristic of the center, and diffuse flash stimulation of the retina does stimulate entire receptive fields, the optic nerve response to diffuse flash would be expected to result from ganglion cell activity characteristic of center stimulation. A diffuse flash should produce virtually no ganglion cell activity characteristic of stimulation of surround alone. Checkerboard patterned stimulation with patterns having a feature size reasonably well matched to receptive field center size should produce ganglion cell activity characteristic of surround stimulation in a number of cells which is approximately equal to the number of cells that respond in a manner characteristic of receptive field center stimulation, and many cells which receive receptive field center stimulation and very little surround stimulation should respond more vigorously than to diffuse flash. Therefore the waveform of the optic nerve response to patterned stimulation can be interpreted as indicating that retinal ganglion cells respond either in smaller number or less vigorously in a manner characteristic of receptive field center stimulation and that the increase in positivity on the late side of the primary positive peak is an indication that a reasonable percentage of the cells which do respond to the stimulation

respond in a manner characteristic of surround stimulation.

The cortical response waveforms for the effective patterned stimuli, 17.5, 31, 55, and 79 minutes of arc per square were each different. The amplitudes of several peaks in the response were effected so as to cause a change in waveshape without any striking change in the overall amplitude of the response. If a different set of retinal ganglion cells in an annular region is stimulated most effectively by each pattern feature size, perhaps the changes in waveshape of the cortical responses to different pattern feature sizes relate to the different locations of the cortical representations of the most stimulated ganglion cells.

Another topic which warrants discussion is that of the effect of defocus of the retinal image upon patterned stimulation. Basically, defocusing a patterned stimulus converts each point of light in the focused image into a blur (spot) circle, the radius of which is proportional to the amount of defocus and the size of the pupil of the eye or, in the case of Maxwellian view stimulation, the diameter of the focal spot at the pupil of the eye. For a given Maxwellian view pattern stimulating instrument, the radius of blur circles produced by a certain dioptric value of defocus is constant and independent of feature size, therefore contrast borders of pattern features are blurred by the same amount independent of the feature size. An amount of blur sufficient to reduce a pattern of small feature size to approximately diffuse stimulation will not reduce a pattern of larger feature size to approximately diffuse stimulation. An example of the effect of a constant amount of defocus upon patterns of different feature

size can be seen in figure 22. Four diopters of defocus were sufficient to reduce the response to a 31 minute of arc pattern to an approximately diffuse response, but the same 4 diopters were not equally effective with a 79 minute of arc pattern.

From the data collected for this dissertation, it was clear that an amount of blurring of contrast borders which is small relative to the size of the features in a patterned stimulus was very ineffective in reducing the response to the patterned stimulus, and that pattern feature size was effective in determining the waveform of the evoked response whether the patterned stimulus was well focused or slightly defocused. There is no evidence in the literature on responses of human subjects to checkerboard patterned stimulation in which several dioptric values of defocus were used (Harter and White, 1968; Harter, 1971) that any consideration was given to the actual relationship of the size of blur circles given by a dioptric value of defocus to the pattern feature sizes used. To determine, for cat, the relationship between blur circle radius and pattern feature size over the whole range of realistic dioptric values of defocus, the schematic eye derived by Vakkur et al. (1963) and a focal spot diameter of 3 mm at the pupil were used to calculate the points through which the curves in figure 34 are drawn. An assumption that the optics of the eye were ideal (MTF = 1.0) was used. Actually, in terms of visual angle, these curves are also valid for experiments with human or monkey when using the same stimulator. Each curve in this figure represents a constant ratio between blur circle radius and pattern feature size. These relationships can be used to determine the effect of a certain dioptric value of defocus which is necessary to create a proportional defocus

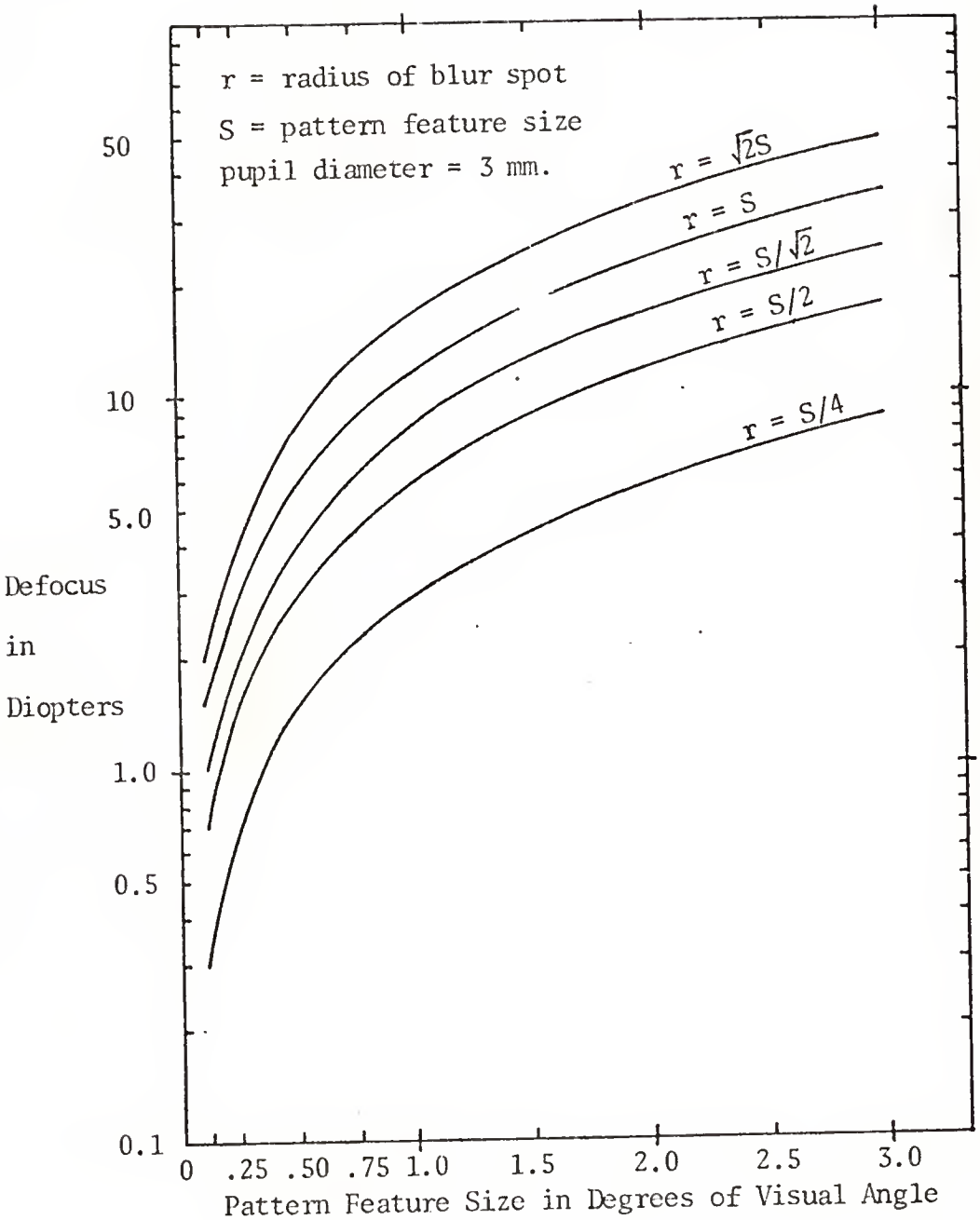


Figure 34. Proportional amounts of Defocus in terms of pattern feature size. Defocusing changes each point of light in a focused image into a blur spot which is proportional in size to the extent of defocus. Each curve represents a constant ratio of blur spot radius to pattern feature size.

effect for a different pattern feature size.

By comparison of figure 19 with the proportional defocus figure, it can be seen that 4 diopters of defocus, which produced blur spots of radius $S/\sqrt{2}$, were necessary to effectively eliminate the sensitivity of the cortical evoked response to a 31 minute of arc pattern. A defocus of 2 diopters, which produced a blur spot radius of S/3 or greater, was only partially effective.

In the paper titled "Effects of Contour Sharpness and Check Size on Visually Evoked Potentials" by Harter and White, human subjects were seated in a darkened chamber and viewed stimuli presented on a translucent screen, under these conditions the diameter of a subject's pupil would be approximately 6 mm and the radius of a blur spot created by a given dioptric value of defocus would be twice as large as the blur spot radius which can be determined from figure 34 (proportional defocus). Therefore, even assuming that the eye has perfect quality optics, the minimum blur spot radius in the retinal images were 10.3 minutes of arc for 1 D (diopter) of error, 20.6 for 2 D, 30.9 for 3 D, and approximately 62 for 6 D. The results published in that paper indicate that visually evoked responses to a 20 minute checkerboard pattern were only slightly effected by a 1 D error, were moderately effected by a 2 D error, and were greatly effected by errors of 3 D or larger. In other words, to produce a moderate degradation of the visually evoked response to checkerboard pattern stimulation these data indicate that an amount of defocus which produces a blur spot radius approximately equal to the pattern check size is necessary. Data from responses to 12 minute, and 46 minute patterns support this finding also.

When an image of a checkerboard pattern is defocused to the extent that light from each point on a contrast border is spread completely across the squares adjacent to the border, it is difficult to speak about contour sharpness since pattern features are practically eliminated in this condition.

From their data Harter and White conclude "the results of this study indicate that certain components of the averaged evoked cortical potential are very sensitive to the sharpness of contour of a patterned visual stimulus and to the size of the elements of the pattern." In terms of the quality of contour sharpness in the retinal image and on the basis of the data from human and from cat it is not possible to agree with this statement. From the point of view of one who is interested in the relationship between the quality of the retinal image and the evoked response to a patterned stimulus, the evoked response is amazingly insensitive to the degree of contour sharpness. It appears that the cortical evoked response is primarily sensitive to pattern feature size and that as feature size is modified or practically eliminated by reduction of contour sharpness the cortical evoked response becomes less characteristic of that to a patterned stimulus and more characteristic of that to a diffuse stimulus. Two points need to be mentioned: (1) Harter and White state that accommodation was not completely controlled during their experiment and (2) certainly perceived contour sharpness and contour sharpness in the retinal image are not identical.

Physiologically, one must influence the activity of retinal ganglion cells before activity is evoked in visual cortex or an image can be perceived. In this sense it is reasonable to interpret the

finding that a relatively large blur of contrast borders is necessary in order to significantly effect the cortical evoked response as an indication that pattern feature size is of greater importance in determining the activity of a retinal ganglion cell than is contour sharpness. It should be noted that in response to defocus of a patterned stimulus the optic nerve response is influenced to approximately the same extent as the cortical evoked response (see figure 22).

Monkey

The quantity of data obtained from the behaving rhesus monkey was very small and can be taken only as an indication of pattern sensitivity of the cortical evoked response. The data obtained from the paralyzed rhesus monkey is strong evidence that the evoked responses of monkey are sensitive to pattern stimulation, at least at the level of visual cortex. Since the same stimulator was used with this animal as with the paralyzed cats the information in the figure concerning the proportional defocus is directly applicable. In general the optics of the eye of man and rhesus monkey are of similar quality and it is significant to note that in this experiment where the animal was adapted to a low photopic level rather than being dark adapted, and where no accommodation was possible, the amount of defocus of contrast borders relative to pattern feature size which was required to eliminate the sensitivity of the evoked response to the patterned stimulus was less than for the human subjects in the work of Harter and White. For example, their results show that 1 D of defocus produced a sight to moderate degradation of the cortical evoked response to a 12 minute checkerboard pattern with human subjects, while the cortical evoked

response of this rhesus to an 11 minute checkerboard pattern was completely degraded by 1.2 D of defocus. A defocus of 1.2 D with an 11 minute checkerboard pattern produced blur spots of radius 0.7 times the side length of a pattern feature, and physically this should be sufficient to effectively eliminate pattern features.

CONCLUSIONS

The primary conclusion of this dissertation is that cat and monkey can be used to study the sensitivity of evoked responses to spatially patterned visual stimulation. This conclusion is based upon the findings that (1) the evoked responses of cat optic nerve and cortex, and monkey cortex are modified in waveform in response to a checkerboard patterned stimulus compared to diffuse stimulation of the same average intensity, (2) these responses are repeatable over hours and weeks, (3) the response waveforms are sensitive to pattern feature size, and (4) the response waveform characteristic of a given patterned stimulus can be reduced to that characteristic of a diffuse stimulus by defocusing the patterned stimulus.

In addition, there is a remarkable correlation between (1) the smallest pattern feature size which is effective in producing evoked responses which are different in waveform from diffuse flash responses, (2) the smallest checkerboard pattern feature size for which any of the fifth harmonic of the fundamental spatial frequency passes through the optics of the cat eye, (3) the histologically determined dendritic field size of retinal ganglion cells in area centralis, and (4) the electrophysiologically determined receptive field center size for ganglion cells in area centralis. This indicates that the spatial selectivity demonstrated by the relatively small sample of ganglion cells from which single unit activity has been recorded is reasonably characteristic of the cells in the population as a whole.

It was also concluded that there is no evidence at the present time to support the statement that the averaged cortical evoked response to a patterned visual stimulus is very sensitive to the sharpness of contrast borders. In terms of the contrast borders in the retinal image, the amount of defocus necessary to have more than a slight effect on an average response to a checkerboard pattern must be sufficient to blur each border approximately half way across each adjacent square and, for different feature sizes, the dioptric value of defocus necessary to obtain comparable effects is proportional to the pattern feature size. A study specifically designed to examine this issue carefully should be performed.

In general, this was an exploratory study. Its positive results provide the basis for many related and/or more detailed projects to gain knowledge of the processing of spatial pattern information in the visual system and to investigate the relationship of single unit activity and evoked responses. The two methods of visual pattern stimulation developed in this research are valuable tools. Specifically, in this project Maxwellian view visual pattern stimulation of paralyzed animals has proven to be a very effective technique. Further development of these methods will provide the means to approach a number of experimental questions.

APPENDIX I

Behavioral Task Training Procedures and Logic Circuit Diagrams

A basic description of the visual fixation task used is given in the methods section of this dissertation. The early training of a monkey is described here.

To train an animal up to the final task after it had accepted sitting and eating or drinking while in a primate chair, the chaired animal was set in the acoustic chamber for longer periods each day for approximately one week. At this point the magazine training of the animal was initiated. During each training session, the chaired animal was placed in the acoustic chamber and viewed through a peep hole by the experimenter. Water rewards were issued to the animal via the drink tube in the chamber when the experimenter judged that the animal was sitting sufficiently still facing forward toward the projection screen. The water rewards were always accompanied by the audible tone which would later be used to signify a correct release of the manipulandum and the duration of the intertrial interval period. The length of time for which the animal was required to sit still facing forward was gradually increased. After several days, program I, which is manually controlled by the experimenter but provides a slight delay between the onset of the tone and an automatically measured reward, was instituted. Only a few training sessions were necessary on program I before transferring to program II. Program II starts with the tone and measured reward as in program I, but in this case the period of the tone is automatically timed and as the tone is turned off, a large

spot of light is presented on the screen. This spot of light remains on the screen until turned off by the experimenter at the end of the trial. As in the previous program, each trial was initiated by the experimenter when the monkey was sitting quietly facing the screen. When the monkey was familiar with this program and sat quietly for periods of up to 30 seconds while the light was on, a new element was added to the system. The manipulandum was placed in the chamber in front of the primate chair. By the method of successive approximations the monkey was taught to reach and pull the manipulandum lever. The experimenter no longer freely initiated trials, but only in response to an attempt as good or better than previous attempts to reach out and pull the manipulandum. Thus at this stage of training the monkey learned that it could initiate a trial which could result in a reward by pulling the manipulandum when all audible and visible cues were absent. Additional pulls during the intertrial interval and light period were not rewarded. There was no penalty time-out at this stage of training, but the light could be left on until the monkey kept its hand off the lever. It was necessary to avoid allowing in any way the animal to associate the manipulandum with turning off the light. When performance with this program was adequate, the monkey was transferred to a simplified version of the final task. The logic program for the final task was modified only in that the variable interval fixation light period was temporarily replaced by a very short fixed interval fixation light period (approximately 100 milliseconds) and the reward period was relatively long. During program II the animal was pulling and very quickly releasing the manipulandum to initiate a trial. It

was now necessary to train the animal to pull and hold the manipulandum until the end of the fixation light (F.L.) period. This was done by making the F.L. period short enough that the animal could not release the lever before the light went off, and then, gradually increasing the duration of the F.L. period so that occasionally when the animal released the lever too soon, it received a time-out. From this the animal discovered that longer holds on the lever were rewarded and very short holds were not. As soon as the animal would perform holds of one-half second with reasonable success, the fixed interval F.L. timing circuit was replaced with the variable interval F.L. timing circuit so as to avoid training the animal to judge any fixed time interval and force it to associate the offset of the F.L. with the proper time to release the lever. The chief element of the variable timing circuit was a film programmer which senses holes punched in a loop of photographic movie film. At first the intervals punched in the film loops were of necessity very short and little variation was permissible if the monkey was to continue to perform with reasonable success, but session after session film loops with slightly longer intervals and a greater range of variability were used until the monkey eventually learned to perform holds of up to 8 seconds duration or greater and to respond accurately to the offset of the fixation light regardless of the variability between intervals. As the animal was being trained to longer and more variable F.L. intervals, the size and intensity of the F.L. spot were gradually reduced and the color of the spot was some days red, some days green, some days white so that finally the animal was forced to fixate very well a small dim spot and

to disregard its color. At this point, all that remained was to gradually introduce the stimulus flashes during the F.L. period. The first stimulus flashes which were presented were dim and infrequent. Gradually they were made more frequent and eventually more intense. Diffuse flashes and checkerboard patterned flashes were used and the animal discovered that the presence or absence of a stimulus flash during the F.L. period had no effect upon its success in performing the task for which it was being rewarded. Always, the time of occurrence of the stimulus flash within the F.L. period was variable. The occurrence and timing of stimulus flashes were controlled by a film loop on a second film programmer. This film loop was constructed so that it could be synchronized with the F.L. period film loop.

A key to logic circuit labels precedes the diagrams which describe the logic of the training programs and the final task. Program I is shown in figure 35, program II in figure 36, and the final visual fixation task program in figures 37 through 43. A subject performed the visual fixation task by operating the manipulandum shown in the fixation light control circuit. The experimenters normal control of this task consisted of choosing the appropriate punched films for the programmers; adjusting the reward system flow resistance; and setting switches to select the reward period, intertrial interval, and time-out durations.

KEY TO LOGIC CIRCUIT LABELS

Abbreviation	Logic Circuit Function
AND	And Gate
B C	Binary Counter
C T	Decimal Counter with Readout
C X	Clean Control Switch
F	Feedback Relay
F F	Flip Flop
F P	Film Programmer
H A	Logic Amplifier
INV	Inverter
M	Manipulandum Switch
MV	Multivibrator
OR	Or Gate
O S	One-Shot
P	Projector
P C	Photocell and Amplifier
RS	Reset Pulse Generator
Switch	Ordinary Switch
SA	Sonalert Tone Generator
SV	Solenoid Valve
Σ	Cummulative Recorder Input

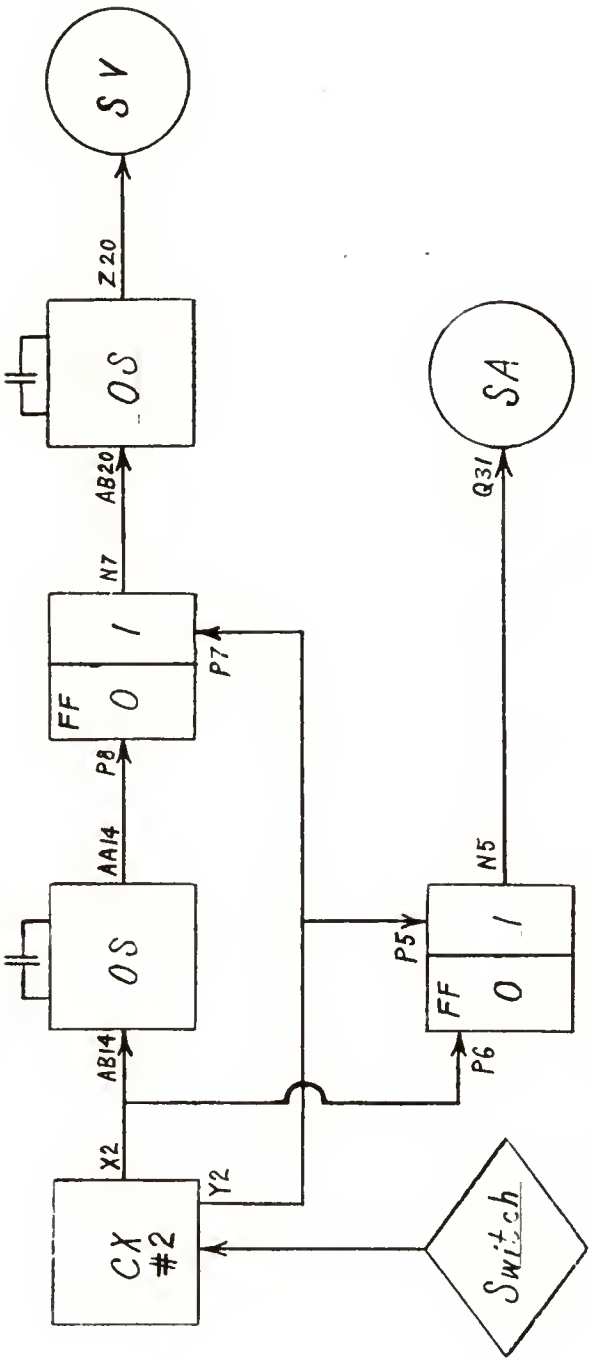


Figure 35. Behavioral training program number 1.

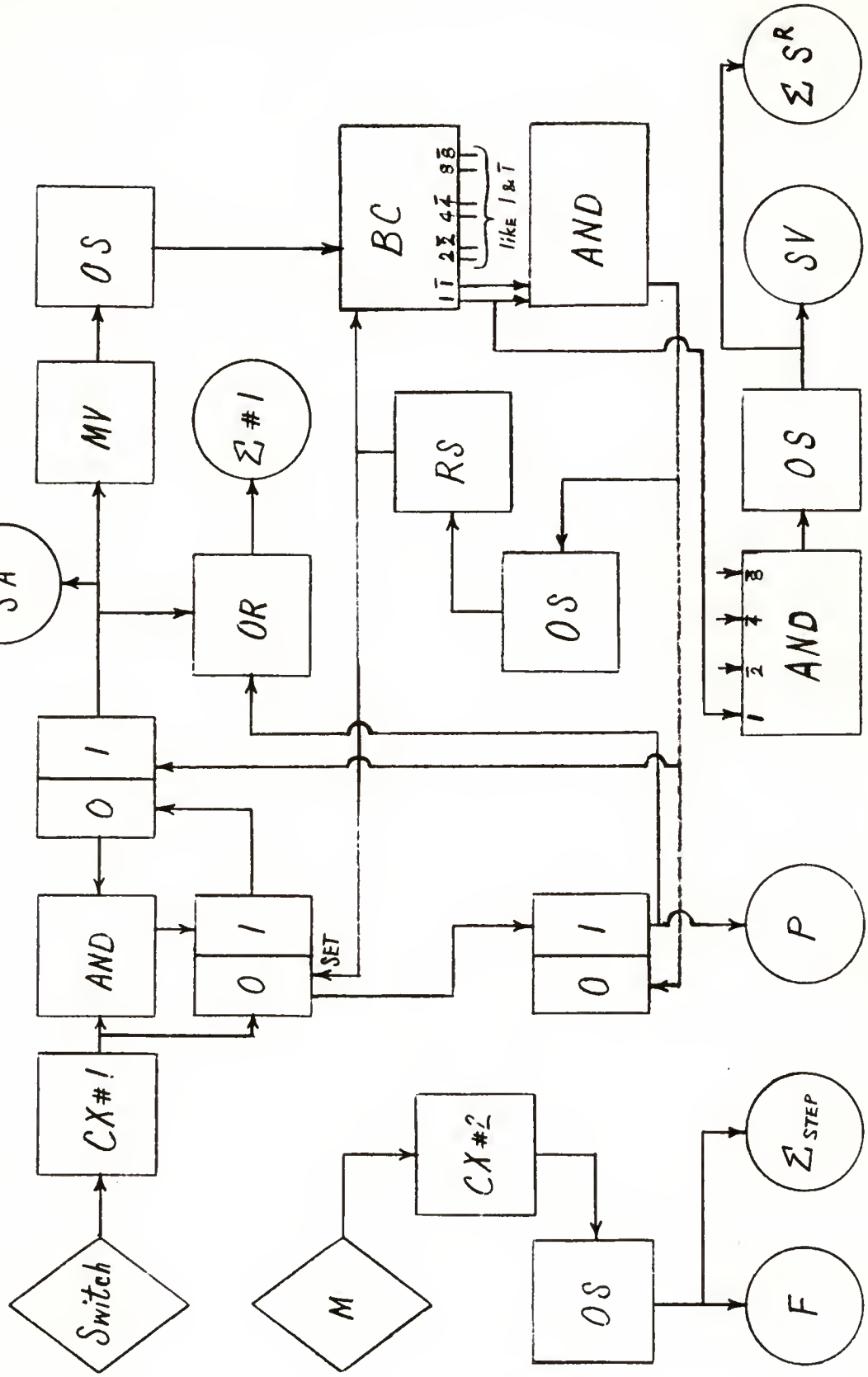
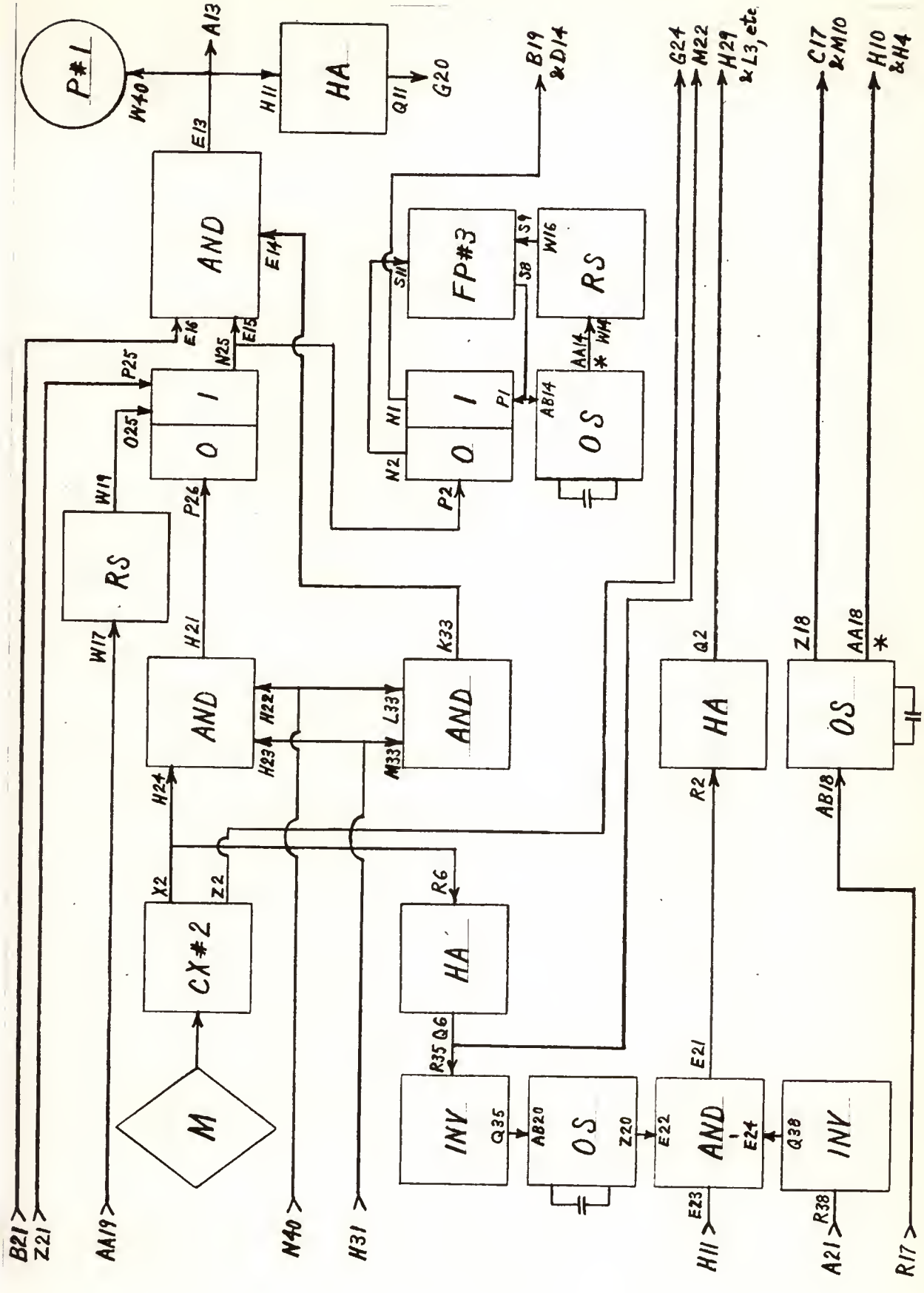


Figure 36. Behavioral training program number 2.

Figure 37. Fixation light control circuit for the visual fixation task.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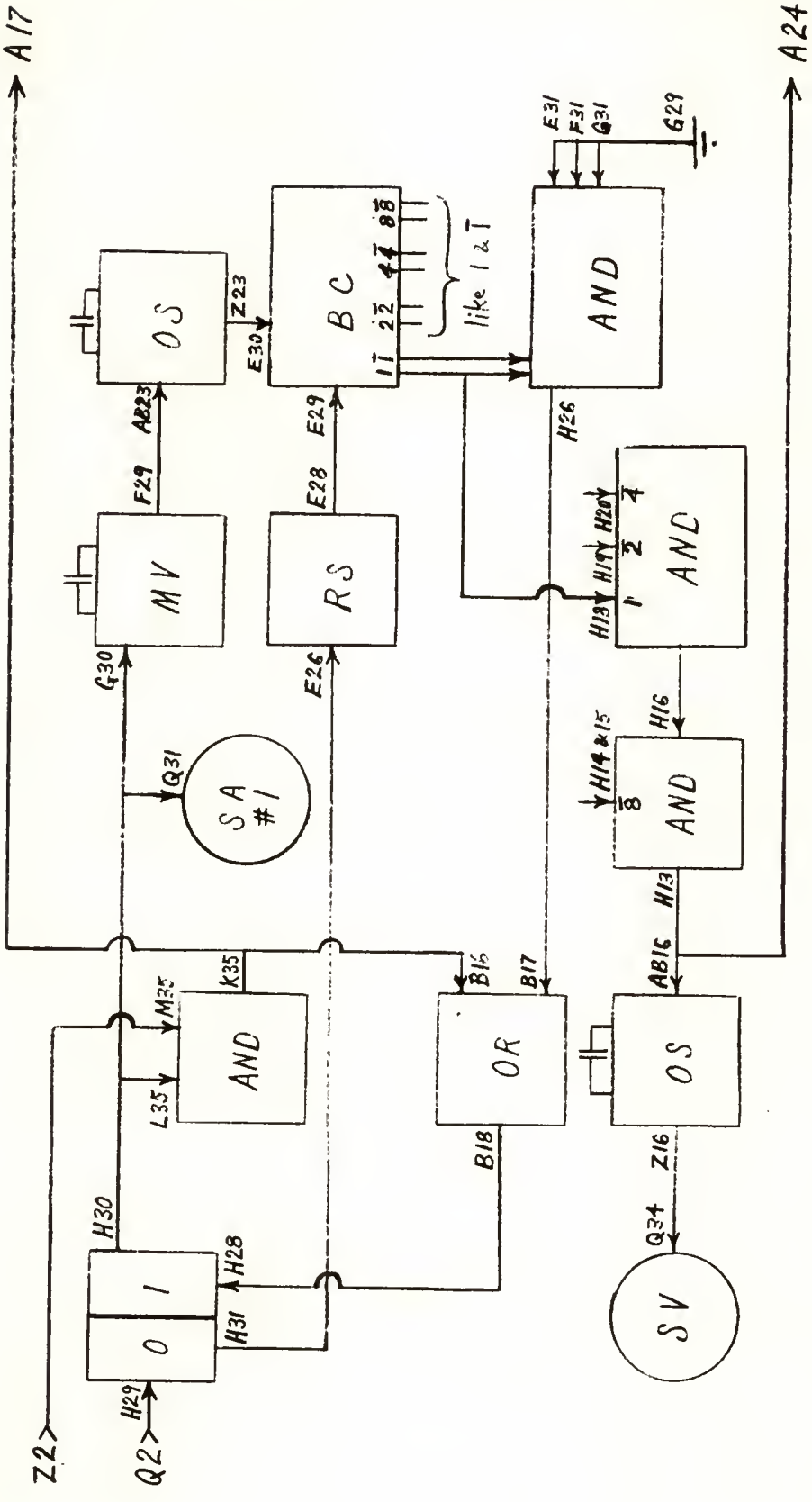


Figure 38. Intertrial interval and reward control circuit for the visual fixation task.

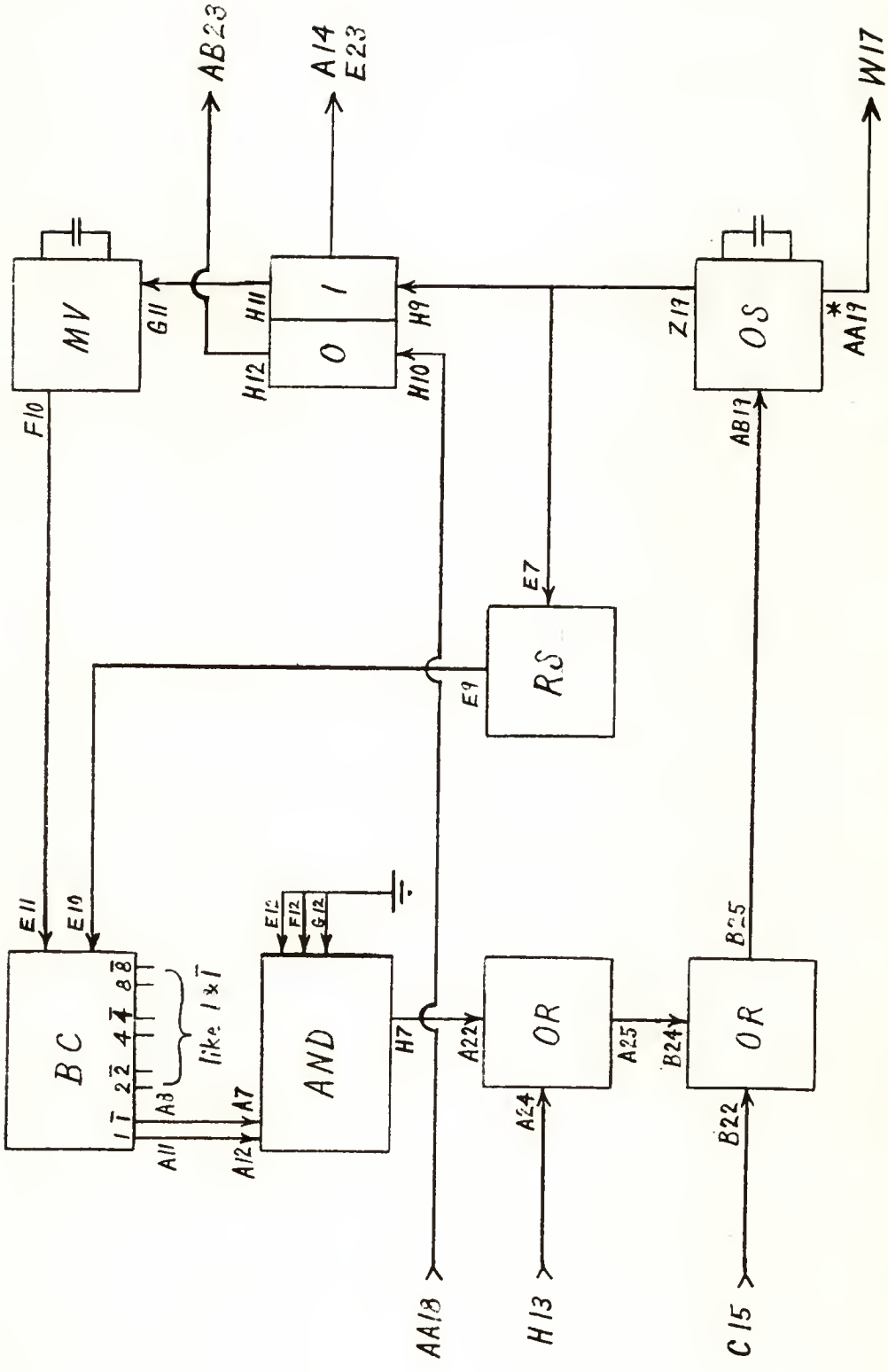


Figure 39. Reward period timer circuit for the visual fixation task.

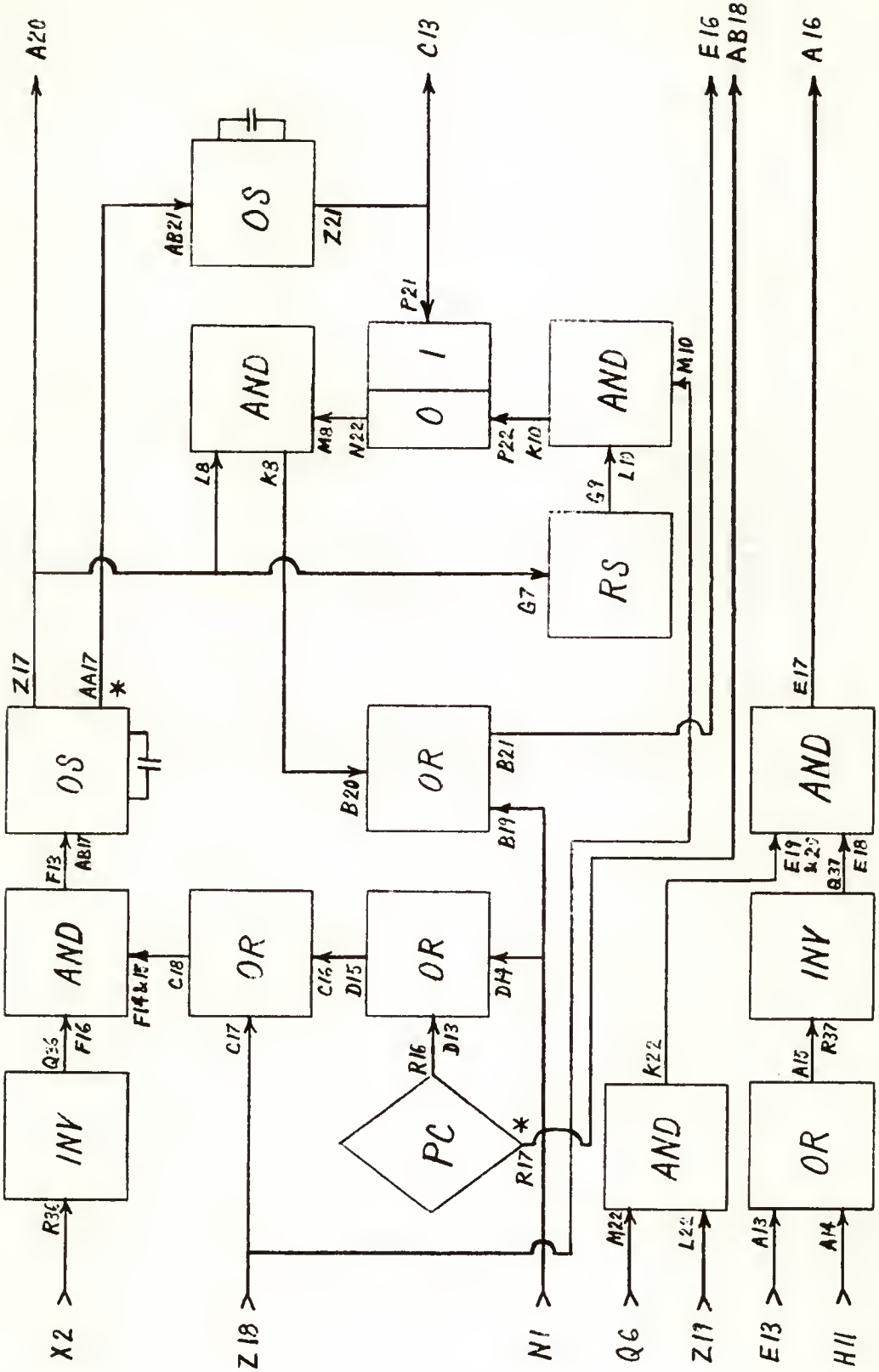
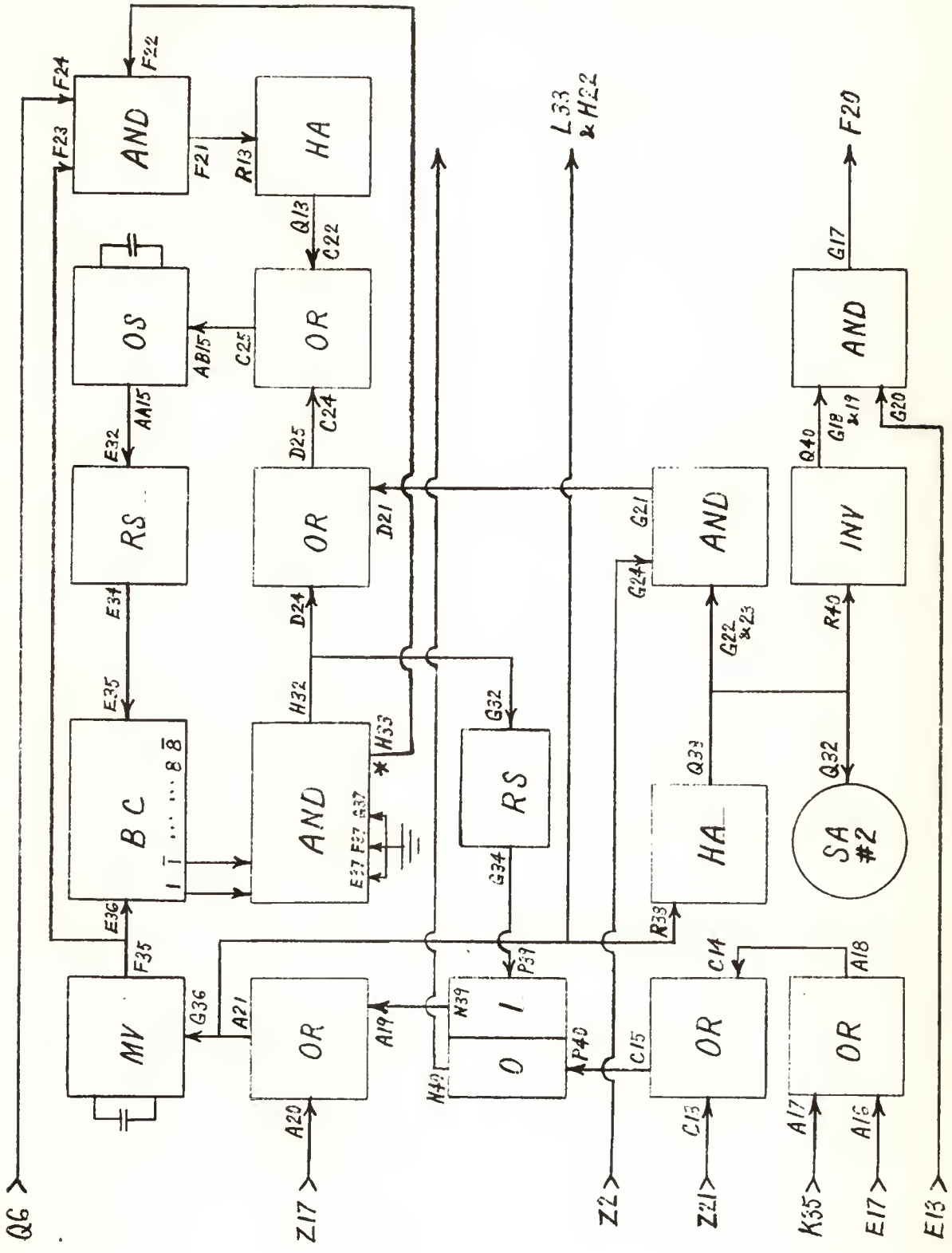


Figure 40. Early release and late release detection circuits for the visual fixation task.

Figure 41. Time-out timer and control circuit for the visual fixation task.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F21
R13
Q13
C22
AB15
C25
A15
E32
C24
D25
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D24
D21
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H32
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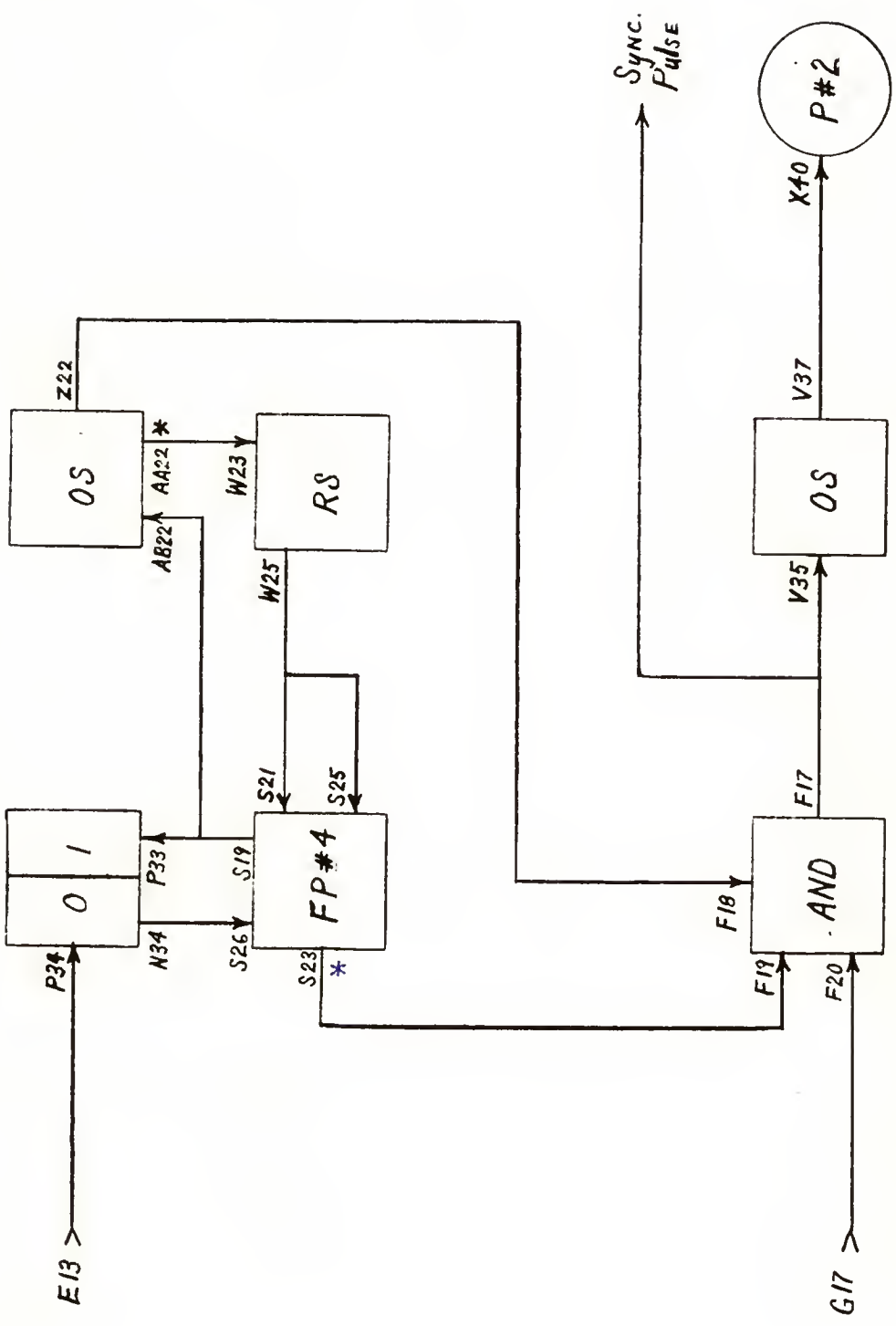


Figure 42. Stimulus flash control circuit for the visual fixation task.

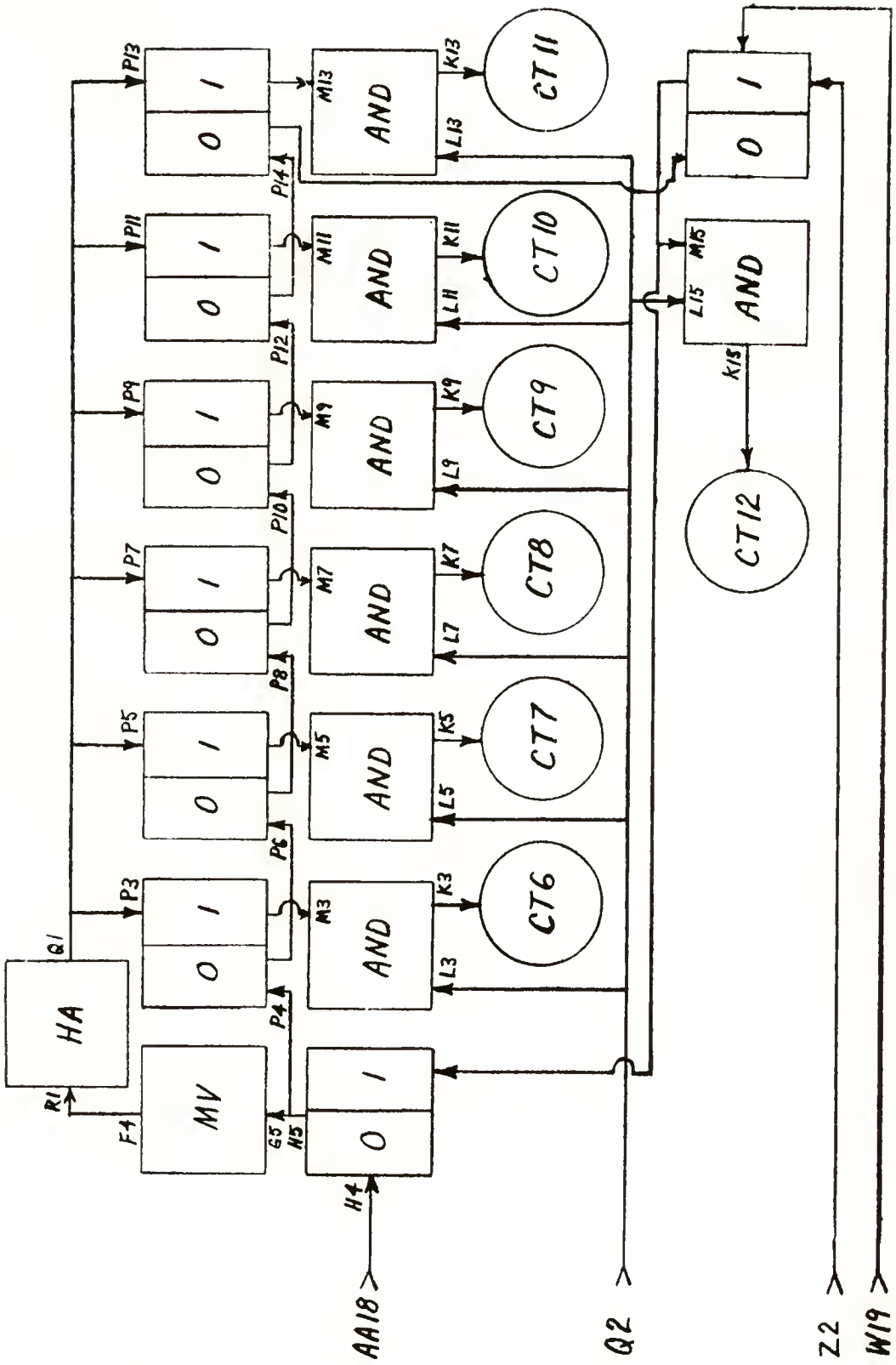


Figure 43. Reaction time ring counter circuit for the visual fixation task.

APPENDIX II

Use of Drugs with Paralyzed Animals

Throughout these experiments an attempt was made to limit the use of drugs to the minimum necessary to restrain the animal and to maintain a steady physiological state as much as possible. A neuromuscular blocking drug was necessary and gallamine triethiodide (Flaxedil) was chosen for this purpose. Since these were not acute experiments, particular care was taken so as not to accumulate excessive amounts of this drug in the animal's body. The disappearance of this drug from the plasma has been shown to follow a 3 time-constant exponential curve (Kalow, 1959; Walts and Dillon, 1968) with the first 20 to 30 minute period after the initial dose having the fastest time-constant, the next approximately 1 hour having the intermediate time-constant, and the period following 1½ hours having the slowest time-constant. In addition, it was known from experience that an initial dose of 5 mg per kg of gallamine administered intravenously was sufficient to block skeletal muscles including the respiratory muscles. For cats, the method which worked well for all experiments included in this dissertation was to use an initial dose of 5 mg per kg administered i.v. followed within approximately 10 minutes by the beginning of an infusion at the rate of 15 mg per kg per hour for 40 minutes to 1 hour, at which time the infusion rate was reduced to approximately 10 mg per kg per hour and maintained for another hour, and then the infusion rate could be reduced to 5 to 7 mg per kg per hour and maintained for the remainder

of the experiment (up to 10 hours duration). The author's limited experience with the use of this drug on rhesus monkey indicates that doses of 70 to 80 percent of that used for cat are sufficient.

As mentioned by Cleland and Enroth-Cugell (1970), the activity and responsiveness of retinal ganglion cells may fall to a low level after several hours if glucose is not contained in the drug solution that is infused. The volume of solution infused is also significant in the sense that it determines to what extent the animal's kidneys filter the drug and its breakdown products from the blood during the experiment (Cohen et al., 1967). The solution infused during these recording sessions was normal or slightly hypotonic saline with 5 percent dextrose and 4 mg per ml of gallamine.

Atropine in doses of 0.3 to 0.4 mg per kg (for cat) was given and repeated after 4 to 5 hours to minimize salivary and respiratory tract secretions while the animal was paralyzed and being respirated.

As a CNS stimulant to prevent the animal from sleeping, amphetamine sulfate was available, but it was rarely used and any data taken after administration of this drug has been so labeled. When used, it was only in mild doses (0.5 to 1.0 mg per kg) and did not produce any noticeable increase in response amplitude. The main effect was to reduce the amplitude of on-going background activity.

At the end of the recording session, an infusion containing the acetylcholine esterase blocker, neostigmine, was used to antagonize the effect of gallamine and accelerate the animal's recovery from paralysis. The maximum dosage given was 25 ng per kg.

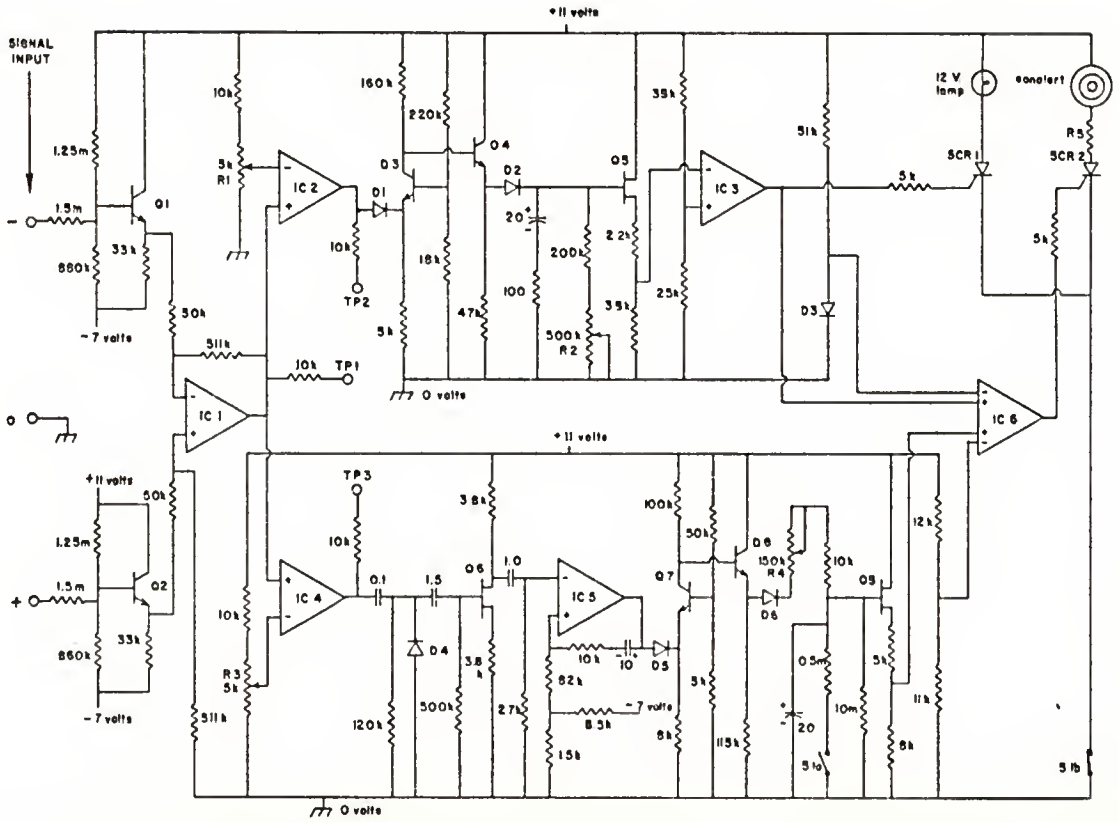
APPENDIX III

Respiration Monitor and Alarm Circuit

This instrument was designed and developed to perform the function that a technician devoting 100 percent of his time and attention to monitoring breath-by-breath indications of end expiratory CO_2 level would serve; it detects CO_2 levels outside of the normal range in either direction. Its notable characteristics are that it is ever present, makes accurate decisions, and alerts the experimenter of possible difficulty at the earliest possible moment after checking several indications to avoid producing unnecessary alarms. When used properly, it has proven to be a valuable and reliable instrument.

A schematic diagram of the circuit used is given in figure 44. An analog signal proportional to CO_2 content of the expired gases is necessary as an input. A signal level of approximately 0.3 volt/percent CO_2 is expected (available from a Beckman model LB-1 CO_2 meter). The signal input terminal leads to a high input impedance differential amplifier containing Q1, Q2, IC1, and related components. The amplified signal is made available to two adjustable threshold comparator circuits (IC2, IC4) and to test point 1 (TP1). IC2 detects crossings of the set lower limit of the normal end expiratory CO_2 range. Each crossing from below to above this limit charges the 20 mfd capacitor following D2 to the maximum it can attain in this circuit. This capacitor continuously discharges at a rate controlled by R2. If the potential across this capacitor ever becomes less than a fixed value (approximately 1/3

Figure 44. Schematic diagram of the respiration monitor and alarm system.



RESPIRATION MONITOR & ALARM

designed by:
H W Doddington

PARTS

IC1 = uA741 operational amplifier
IC2,3,4,5 = uA710 comparator
IC6 = uA711 dual comparator

Q1,2,3,4,7,8 = 2N3643
Q5,6,9 = 2N5163

D1,2,3,4,5,6 = 1N4008

SCR1,2 = C106A1

S1 = DPDT (reset switch shown in operate position)

CONTROLS

R1 sets lower limit.
R2 sets time allowed below lower limit before activating the alarm.
R3 sets upper limit.
R4 sets number of violations of the upper limit tolerable per unit time.
R5 controls volume of audio from sonalert.

maximum potential), it is detected by comparator IC3 and the low level warning light and audible alarm are activated.

IC4 detects crossings of the set upper limit of the normal range. Each crossing from below to above this limit triggers a one-shot (IC5, etc.) to deliver a pulse of current to the 20 mfd capacitor which is attached to the gate of FET Q9. The magnitude of this current pulse is controlled by R4. Current pulses are integrated on this capacitor and the stored charge decays at a rate determined by the 10 megohm parallel resistance. If the potential across this capacitor ever rises to a fixed value (approximately 1/3 of the potential available at the cathode of D6 during a pulse), it is detected by comparator IC6 and the audible alarm is activated without the light.

The outputs of the lower and upper limit crossing detectors are available at TP2 and TP3 respectively for ease in adjusting these settings. Depending upon the settings of R2 and R4, temporary high or low CO_2 conditions can be accepted without generating an alarm. Once activated, the light and/or alarm remain on until the reset switch is operated.

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BIOGRAPHICAL SKETCH

Harold William Doddington was born in St. Joseph, Michigan, on January 18, 1942. He is the son of Harold E. and Charlotte K. Doddington. He grew up in Hallandale, Florida, and attended South Broward High School. He played trombone in the high school band for 4 years and was an amateur radio operator. Upon graduation from high school in 1959, he entered the University of Florida to major in electrical engineering. From 1960 through 1963, he participated in the cooperative engineering education program working with the Federal Communications Commission at the district field office in Miami, Florida, as a student engineer.

He received the first Sustained Superior Performance Award ever issued by the FCC to a student employee. He spent the summer of 1962 youth hosteling in Western Europe. In August, 1964, he received the degree Bachelor of Electrical Engineering from the University of Florida and was employed as a member of the technical staff by ITT Caribbean Manufacturing, Research and Development Laboratory, Rio Piedras, Puerto Rico. In September of 1965, he returned to the University of Florida to accept a Graduate School Fellowship and in August of 1966 he was awarded the degree Master of Engineering. Because of a strong interest in the interaction between applied physical sciences and medical sciences, he entered a doctoral program in the Physiology Department of the College of Medicine. He became associated with the Visual Sciences Laboratory,

an interdisciplinary group, and developed research related to the processing of spatial pattern information in the visual system. He received a one year traineeship in physiology and then a pre-doctoral fellowship in the Center for Neurobiological Sciences.

In 1965, Harold William Doddington married the former Claudia Anna Walker. She holds the degree Master of Science in Engineering. They have one daughter, Hally Katheryn.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

William W. Dawson, Chairman
Professor of Physiology

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Arthur B. Otis
Professor of Physiology

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Robert L. King
Assistant Professor of Physiology

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Calvin K. Adams
Assistant Professor of Psychology

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Arnold H. Nevis
Professor of Electrical Engineering

This dissertation was submitted to the Dean of the College of Medicine and to the Graduate Council, and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

August, 1972

Dean, College of Medicine

Dean, Graduate School